

Bioconductor's Computational Ecosystem for Genomic Data Science in Cancer

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Abstract

The Bioconductor project enters its third decade with over two thousand packages for genomic data science, over 100,000 annotation and experiment resources, and a global system for convenient distribution to researchers. Over 60,000 PubMed Central citations and terabytes of content shipped per month attest to the impact of the project on cancer genomic data science. This report provides an overview of cancer genomics resources in Bioconductor. After an overview of Bioconductor project principles, we address exploration of institutionally curated cancer genomics data such as TCGA. We then review genomic annotation and ontology resources relevant to cancer and then briefly survey Analytical workflows addressing specific topics in cancer genomics. Concluding sections cover how new software and data resources are brought into the ecosystem and how the project is tackling needs for training of the research workforce. Bioconductor's strategies for supporting methods developers and researchers in cancer genomics are evolving along with experimental and computational technologies. All the tools described in this report are backed by regularly maintained learning resources that can be used locally or in cloud computing environments.

1 Introduction

Computation is a central component of cancer genomics research. Tumor sequencing is the basis of computational investigation of mutational, epigenetic and immunologic processes associated with cancer initiation and progression. Numerous computational workflows have been produced to profile tumor cell transcriptomes and proteomes. New technologies promise to unite sequence-based characterizations with digital histopathology, ultimately driving efforts in molecule design and evaluation to produce patient-centered treatments.

Bioconductor is an open source software project with a 20 year history of uniting biostatisticians, bioinformaticians, and genome researchers in the creation of an ecosystem of data, annotation, and analysis resources for research in genome-scale biology. This paper will review current

approaches of the project to advancing cancer genomics. After a brief discussion of basic principles of the Bioconductor project, we will present a “top down” survey of resources useful for cancer bioinformatics. Primary sections address

- how to explore institutionally curated cancer genomics data
- genomic annotation resources relevant to cancer genomics
- analytical workflows
- components for introducing new data or analyses
- pedagogics and workforce development.

Appendix 1 (section 10) of this paper includes descriptions of 69 Bioconductor software packages that use the term “cancer” in their package metadata.

Appendix 2 (section 11) of this paper includes descriptions of 63 Bioconductor experimental data packages that use the term “cancer” in their package metadata.

2 Bioconductor principles

2.1 R packages and vignettes

Software tools and data resources in Bioconductor are organized into “R packages”. These are collections of folders with data, code (principally R functions), and documentation following a protocol specified in [Writing R Extensions](#). R packages have a DESCRIPTION file with metadata about package contents and provenance. Package structure can be checked for validity using the R CMD check facility. Documentation of code and data can be programmatically checked for existence and validity. The DESCRIPTION file for a package specifies its version and also gives precise definition of how an R package may depend upon versions of other packages.

At its inception, Bioconductor introduced a new approach to holistic package documentation called “vignette”. Vignettes provide narrative and explanation interleaved with executable code describing package operations. While R function manual pages describe the operation of individual functions, vignettes illustrate the interoperation of package components and provide motivation for both package design but also context for its use.

2.2 R package repositories; repository evolution

Bioconductor software forms a coherent ecosystem that can be checked for consistency of versions of all packages available in a given installation of R. Bioconductor packages may specify dependency on other Bioconductor packages, or packages that are available in the CRAN repository. Bioconductor does not include packages with dependencies on “github-only” packages. Later in this paper we will provide details on package quality assurance that provide a rationale for this restriction.

Major updates to the R language occur annually, and updates are preceded by careful assessment of effects of language change on Bioconductor package operations. These effects can be identified through changes in the output of R CMD check. The Bioconductor ecosystem is updated twice a year, once to coincide with update to R, and once about six months later. The semianual updates reflect the need to track developments in the fast-moving field of genomic data science.

2.3 Package quality assessment; installation consistency

The BiocCheck function is used to provide more stringent assessment of package compliance with basic principles of the Bioconductor ecosystem.

The BiocManager package provides for installing and updating package and has functionality for verifying the coherence and version status of the currently installed package collection. This is important in the context of a language and package ecosystem that changes every six months, while analyses may take years to complete. Tools for recreating past package collections are available to assist in reproducing outputs of prior analyses.

2.4 Unifying assay and sample data: SummarizedExperiment and MultiAssayExperiment

Most of the data from genome-scale experiments to be discussed in this chapter are organized in special data containers rooted in the concepts of the SummarizedExperiment class. Briefly, assay data are thought of as occupying a $G \times N$ array, and sample level data occupy an $N \times K$ table. The array and the table are linked together in the SummarizedExperiment; see Figure 1.

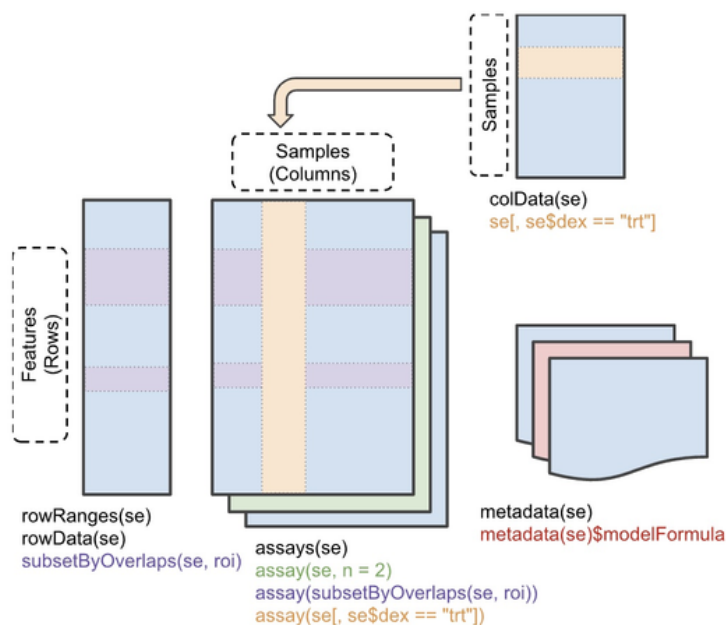


Figure 1: SummarizedExperiment schematic.

Multiple representations of assay results may be managed in this structure, but all assay arrays must have dimensions $G \times N$.

For experiment collections in which the same samples are subjected to multiple genome-scale assays, MultiAssayExperiment containers are used. See Figure 2 for the layout.

Further details on these data structures will be provided in section 6.

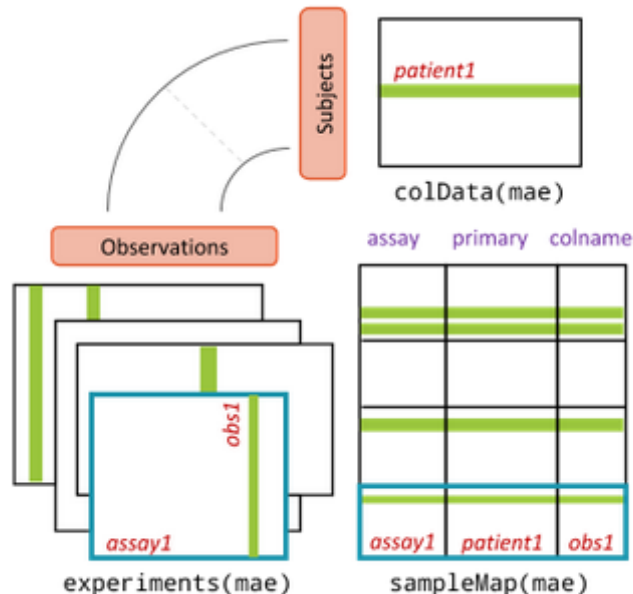


Figure 2: MultiAssayExperiment schematic.

2.5 Downloading and caching cancer genomics data and annotations

Downloading and managing data from various online resources can be excessively time consuming. Bioconductor encourages data caching for increased efficiency and reproducibility. The caching data methods employed in Bioconductor allow analysis code to concisely refer to data resources as needed, with minimal attention to how data are stored, retrieved or transformed. It allows for easy management and reuse of data that are on remote servers or in cloud, storing source location and providing information for data updates. The BiocFileCache Bioconductor package handles data management from within R.

BiocFileCache is a general-use caching system but Bioconductor also provides “Hubs”, AnnotationHub and ExperimentHub, to help distributed annotation or experimental data hosted externally. Both AnnotationHub and ExperimentHub use BiocFileCache to handle download and caching of data.

AnnotationHub provides a centralized repository of diverse genomic annotations, facilitating easy access and integration into analyses. Researchers can seamlessly retrieve information such as genomic features, functional annotations, and variant data, streamlining the annotation process for their analyses.

ExperimentHub extends this concept to experimental data. It serves as a centralized hub for storing and sharing curated experiment-level datasets, allowing researchers to access a wide range of experimental designs and conditions. This cloud-based infrastructure enhances collaboration and promotes the reproducibility of analyses across different laboratories.

The curatedTCGAData package provides some resources through ExperimentHub, as do many other self-identified “CancerData” resources. Once the ExperimentHub is loaded, it can be queried for terms of interest.

```
{r useeh} <!-- , fig.cap="ExperimentHub attachment, retrieval, query, and response  
when seeking cancer-related data.", message=FALSE} --> library(ExperimentHub) eh <-  
ExperimentHub() query(eh, "CancerData")
```

Multiple terms can be used to narrow results before choosing a download.

```
query(eh, c("cancerData", "esophageal"))  
## ExperimentHub with 2 records  
## # snapshotDate(): 2023-10-24  
## # $dataProvider: University of California San Francisco  
## # $species: Homo sapiens  
## # $rdataclass: RangedSummarizedExperiment, data.frame  
## # additional mcols(): taxonomyid, genome, description,  
## # coordinate_1_based, maintainer, rdatadateadded, preparerclass, tags,  
## # rdatapath, sourceurl, sourcetype  
## # retrieve records with, e.g., 'object[["EH8527"]]'  
##  
##           title  
## EH8527 | cao_esophageal_wgbs_hg19  
## EH8530 | cao_esophageal_transcript_counts
```

Similarly AnnotationHub files can be downloaded for annotating data. For example, the ensembl 110 release of gene and protein annotations are obtained with the following:

```
library(AnnotationHub)  
ah <- AnnotationHub()  
tag = names(query(ah, c("Ensembl", "110", "Homo sapiens")))  
ens110 <- ah[[tag]]
```

3 Exploring institutionally curated cancer genomics data

3.1 The Cancer Genome Atlas

An overview of Bioconductor's resource for the Cancer Genome Atlas (TCGA) is easy to obtain, with the curatedTCGADData package.

```
library(curatedTCGADData)  
tcgatab = curatedTCGADData(version="2.1.1")
```

Records obtained for adrenocortical carcinoma (code ACC) are in Table 1.

Various conventions are in play in this table. The "title" field is of primary concern. The title string can be decomposed into substrings with interpretation [tumorcode]_[assay]_[date]_[optional codes]. The column `ah_id` will be explained in section 4, and entries in column `rdataclass` will be discussed in section 6 below.

3.1.1 Tumor code resolution

There are 33 different tumor types available in TCGA. The decoding of tumor codes for the first ten in alphabetical order is provided in Table 2.

Table 1: Records returned by `curatedTCGAData::curatedTCGAData()`, filtered to those pertaining to adrenocortical carcinoma.

	ah_id	title	file_size	rdataclass
1	EH4737	ACC_CNASNP-20160128	0.8 Mb	RaggedExperiment
2	EH4738	ACC_CNVSNP-20160128	0.2 Mb	RaggedExperiment
3	EH4740	ACC_GISTIC_AllByGene-20160128	0.2 Mb	SummarizedExperiment
4	EH4741	ACC_GISTIC_Peaks-20160128	0 Mb	RangedSummarizedExperiment
5	EH4742	ACC_GISTIC_ThresholdedByGene-20160128	0.2 Mb	SummarizedExperiment
6	EH4744	ACC_Methylation-20160128_assays	239.2 Mb	SummarizedExperiment
7	EH4745	ACC_Methylation-20160128_se	6 Mb	RaggedExperiment
8	EH4747	ACC_Mutation-20160128	0.7 Mb	SummarizedExperiment
9	EH4748	ACC_RNASeq2Gene-20160128	2.7 Mb	SummarizedExperiment
10	EH4750	ACC_RPPAArray-20160128	0.1 Mb	SummarizedExperiment
414	EH8118	ACC_miRNASeqGene-20160128	0.2 Mb	SummarizedExperiment
415	EH8119	ACC_RNASeq2GeneNorm-20160128	5.4 Mb	SummarizedExperiment

3.1.2 Assay codes and counts

Assays performed on tumors vary across tumor types. For assay types shared between breast cancer, glioblastoma, and lung adenocarcinoma (code LUAD), the numbers of tumor and normal samples available in `curatedTCGAData` are provided in Table 3.

3.1.3 An example dataset for RNA-seq from glioblastoma multiforme

We obtain normalized RNA-seq data on primary tumor samples for GBM with

```
gbrna = TCGAPrimaryTumors(curatedTCGAData("GBM",
  "RNASeq2GeneNorm", dry.run=FALSE, version="2.1.1"))
gbrna
## A MultiAssayExperiment object of 1 listed
## experiment with a user-defined name and respective class.
## Containing an ExperimentList class object of length 1:
## [1] GBM_RNASeq2GeneNorm-20160128: SummarizedExperiment with 18199 rows and 153 columns
## Functionality:
## experiments() - obtain the ExperimentList instance
## colData() - the primary/phenotype DataFrame
## sampleMap() - the sample coordination DataFrame
## `$`, `[`, `[[]` - extract colData columns, subset, or experiment
## *Format() - convert into a long or wide DataFrame
## assays() - convert ExperimentList to a SimpleList of matrices
## exportClass() - save data to flat files
```

R functions defined in Bioconductor packages can operate on the variable `gbrna` to retrieve information of interest. Details on the underlying data structure are given in section 6 below. For most assay types, we think of the quantitative assay information as tabular in nature, with table rows corresponding to genomic features such as genes, and table columns corresponding to samples.

Information on GBM samples employs the `colData` function.

Table 2: Decoding TCGA tumor code abbreviations.

Code	Tumor.Type
ACC	Adrenocortical Carcinoma
BLCA	Bladder Urothelial Carcinoma
BRCA	Breast Invasive Carcinoma
CESC	Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma
CHOL	Cholangiocarcinoma
CNTL	Controls
COAD	Colon Adenocarcinoma
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
ESCA	Esophageal Carcinoma
FPPP	FFPE Pilot Phase II
GBM	Glioblastoma Multiforme
HNSC	Head and Neck Squamous Cell Carcinoma
KICH	Kidney Chromophobe
KIRC	Kidney Renal Clear Cell Carcinoma
KIRP	Kidney Renal Papillary Cell Carcinoma
LAML	Acute Myeloid Leukemia
LCML	Chronic Myelogenous Leukemia
LGG	Brain Lower Grade Glioma
LIHC	Liver Hepatocellular Carcinoma
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
MESO	Mesothelioma
MISC	Miscellaneous
OV	Ovarian Serous Cystadenocarcinoma
PAAD	Pancreatic Adenocarcinoma
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate Adenocarcinoma
READ	Rectum Adenocarcinoma
SARC	Sarcoma
SKCM	Skin Cutaneous Melanoma
STAD	Stomach Adenocarcinoma
TGCT	Testicular Germ Cell Tumors
THCA	Thyroid Carcinoma
THYM	Thymoma
UCEC	Uterine Corpus Endometrial Carcinoma
UCS	Uterine Carcinosarcoma
UVM	Uveal Melanoma

```
dim(colData(gbrna))
## [1] 153 4380
```

For sample level information obtained `colData`, we think of rows as samples, and columns as sample attributes.

Table 3: Numbers of assays available in TCGA on tumor and normal samples, for breast cancer, glioblastoma, and lung adenocarcinoma.

	BRCA	BRCAnormal	GBM	GBMnormal	LUAD	LUADnormal
CNASNP	1089	1120	577	527	516	579
CNVSNP	1080	1119	577	527	516	579
GISTIC_AllByGene	1080	0	577	0	516	0
GISTIC_Peaks	1080	0	577	0	516	0
GISTIC_ThresholdedByGene	1080	0	577	0	516	0
Mutation	988	5	283	7	230	0
RNASeq2Gene	1093	119	153	13	515	61
RPPAArray	887	50	233	11	365	0
RNASeq2GeneNorm	1093	119	153	13	515	61
Methylation_methyl27	314	29	285	0	65	24
Methylation_methyl450	783	102	140	14	458	34

3.1.4 Clinical and phenotypic data

TCGA datasets are generally provided as combinations of results for tumor tissue and normal tissue. The determination of a record's sample type is encoded in the sample "barcode". Decoding of sample barcodes is described at the [Genomic Data Commons Encyclopedia](#) with specific interpretation of sample types listed [separately](#). The TCGAutils package provides utilities for extracting data on primary tumor samples, excluding samples that may have been taken on normal tissue or metastases.

Clinical and phenotypic data on all TCGA samples are voluminous. For example, there are 2684 fields of sample level data for BRCA samples, and 4380 fields for GBM samples. Many of these fields are meaningfully populated for only a very small minority of samples. To see this for GBM:

```
mean(sapply(colData(gbrna), function(x) mean(is.na(x))>.90))
## [1] 0.8091324
```

In words, for 81% of clinical data fields in TCGA GBM data, at least 90% of entries are missing.

Nevertheless, with careful inspection of fields and contents, nearly complete clinical data can be extracted and combined with molecular and genetic assay data with modest effort.

The following code chunk illustrates a very crude approach to comparing survival profiles for BRCA, GBM, and LUAD donors. The result is in Figure 3.

```
# obtain mutation data for BRCA, GBM, LUAD; could use any or all assay types
brmut = curatedTCGAData("BRCA", "Mutation", version = "2.1.1", dry.run = FALSE)
gbmut = curatedTCGAData("GBM", "Mutation", version = "2.1.1", dry.run = FALSE)
lumut = curatedTCGAData("LUAD", "Mutation", version = "2.1.1", dry.run = FALSE)
# extract survival times
library(survival)
getSurv = function(mae) {
  days_on = with(colData(mae), ifelse(is.na(days_to_last_followup),
    days_to_death, days_to_last_followup))
```



```
Surv(days_on, colData(mae)$vital_status)
}
ss = lapply(list(brmut, gbmut, lumut), getSurv)
codes = c("BRCA", "GBM", "LUAD")
type = factor(rep(codes, sapply(ss,length)))
allsurv = do.call(c, ss)
library(GGally)
ggsurv(survfit(allsurv~type))
```

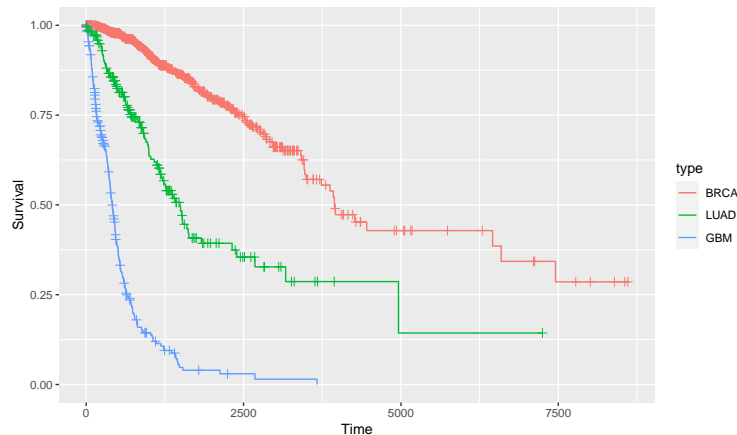


Figure 3: Survival profile extraction from three MultiAssayExperiments produced with curatedTCGAData calls.

At this point, survival times within tumor type can be stratified by any features of the mutation profiles of individual samples. The “RaggedExperiment” class is employed to test each BRCA sample for presence of any mutation in the gene TTN. See Figure 4.

```
bprim = TCGAPrimaryTumors(brmut)
## harmonizing input:
## removing 5 sampleMap rows with 'colname' not in colnames of experiments
mutsyms = assay(experiments(bprim)[[1]], "Hugo_Symbol")
cn = rownames(colData(bprim)) # short
cna = colnames(mutsyms) # long
cnas = substr(cna, 1, 12)
hasTTNmut = apply(assay(experiments(TCGAPrimaryTumors(brmut))[[1]], "Hugo_Symbol"),
  2, function(x) length(which(x=="TTN"))>0)
## harmonizing input:
## removing 5 sampleMap rows with 'colname' not in colnames of experiments
names(hasTTNmut) = cnas
bsurv = getSurv(TCGAPrimaryTumors(brmut))
## harmonizing input:
## removing 5 sampleMap rows with 'colname' not in colnames of experiments
hasTTNmut = hasTTNmut[cn] # match mutation records to surv times
ggsurv(survfit(bsurv~hasTTNmut))
```

Similar manipulations permit exploration of relationships between any molecular assay outcomes and any clinical data collected in TCGA.

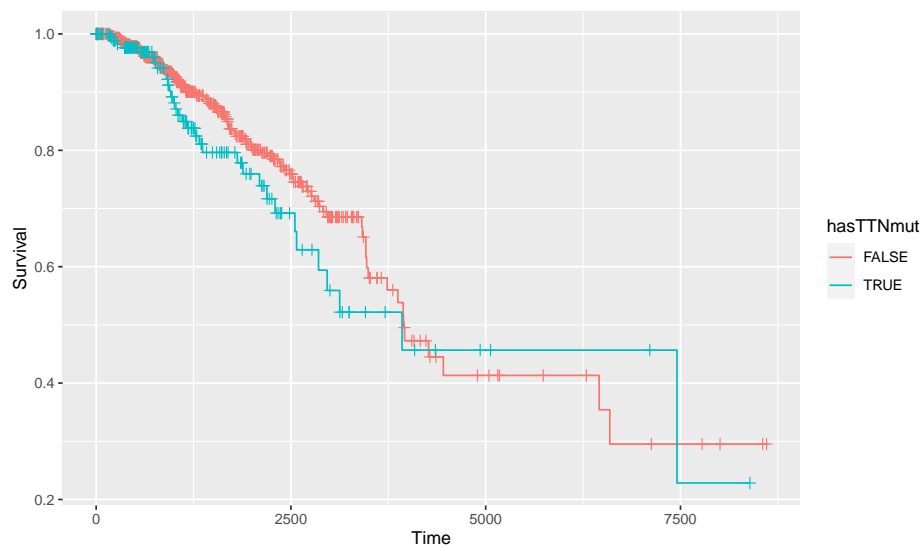


Figure 4: Survival distributions for donors of breast tumors in TCGA, stratified by presence or absence of mutation in gene TTN.

3.2 cBioPortal

The [cBioPortal](#) user guide defines the goal of the portal to be reducing “the barriers between complex genomic data and cancer researchers by providing rapid, intuitive, and high-quality access to molecular profiles and clinical attributes from large-scale cancer genomics projects, and therefore to empower researchers to translate these rich data sets into biologic insights and clinical applications.”

Bioconductor’s `cBioPortalData` package simplifies access to over 300 genomic studies of diverse cancers in cBioPortal. The main unit of data access is the publication. The `cBioPortal` function mediates a connection between an R session and the cBioPortal API. `getStudies` returns a tibble with metadata on all studies.

```
library(cBioPortalData)
cbio = cBioPortal()
allst = getStudies(cbio)
dim(allst)
## [1] 397 13
```

A pruned selection of records from the cBioPortal studies table is given in Table 4.

Table 4: Excerpts from four fields on selected records in the cBioPortal `getStudies` output

name	description	studyId
Adenoid Cystic Carcinoma of the Breast	Whole exome sequencing of 12 breast AdCCs.	acbc_mskcc_2015
Adenoid Cystic Carcinoma	Whole-exome or whole-genome sequencing analysis of 60 ACC tumor/normal pairs	acyc_mskcc_2013
Adenoid Cystic Carcinoma	Targeted Sequencing of 28 metastatic Adenoid Cystic Carcinoma samples.	acyc_fmi_2014

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Adenoid Cystic Carcinoma	Whole-genome or whole-exome sequencing of 25 adenoid cystic carcinoma tumor/normal pairs.	acyc_jhu_2016
Adenoid Cystic Carcinoma	WGS of 21 salivary ACCs and targeted molecular analyses of a validation set (81 patients).	acyc_mda_2015
Adenoid Cystic Carcinoma	Whole-genome/exome sequencing of 10 ACC PDX models.	acyc_mgh_2016
Adenoid Cystic Carcinoma	Whole exome sequencing of 24 ACCs.	acyc_sanger_2013
Adenoid Cystic Carcinoma Project	Multi-Institute Cohort of 1045 Adenoid Cystic Carcinoma patients.	acc_2019
Basal Cell Carcinoma	Whole-exome sequencing of 126 basal cell carcinoma tumor/normal pairs; targeted sequencing of 163 sporadic samples (40 tumor/normal pairs) and 4 Gorlin syndrome basal cell carcinomas.	bcc_unige_2016

To explore copy number alteration data from a study on angiosarcoma, we find the associated studyId field in `allst` and use the `cBioDataPack` function to retrieve a `MultiAssayExperiment`:

```
ann = "angs_projectPainter_2018"
ang = cBioDataPack(ann)
## Warning in .find_with_xfix(df_colnames, get(paste0(fix, 1)), get(paste0(fix, :
## Multiple prefixes found, using keyword 'region' or taking first one

## Warning in .find_with_xfix(df_colnames, get(paste0(fix, 1)), get(paste0(fix, :
## Multiple prefixes found, using keyword 'region' or taking first one
ang
## A MultiAssayExperiment object of 3 listed
## experiments with user-defined names and respective classes.
## Containing an ExperimentList class object of length 3:
## [1] cna_hg19.seg: RaggedExperiment with 27835 rows and 48 columns
## [2] cna: SummarizedExperiment with 23109 rows and 48 columns
## [3] mutations: RaggedExperiment with 24058 rows and 48 columns
## Functionality:
## experiments() - obtain the ExperimentList instance
## colData() - the primary/phenotype DataFrame
## sampleMap() - the sample coordination DataFrame
## `$`, `[`, `[[]` - extract colData columns, subset, or experiment
## *Format() - convert into a long or wide DataFrame
## assays() - convert ExperimentList to a SimpleList of matrices
## exportClass() - save data to flat files
```

The copy number alteration outcomes are in the `assay` component of the experiment.

```
seg = experiments(ang)[[1]]
colnames(seg) = sapply(strsplit(colnames(seg), "-"), "[", 5)
assay(seg)[1:4,1:4]
## DAE1F DACME DADBW DAD34
```

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```
## 1:12227-955755      71    NA    NA    NA
## 1:957844-1139868    62    NA    NA    NA
## 1:1140874-1471177  167    NA    NA    NA
## 1:1475170-1855370  113    NA    NA    NA
```

The rownames component of this matrix can be transformed to a GenomicRanges instance for concise manipulation.

```
library(GenomicRanges)
## 0/0 packages newly attached/loaded, see sessionInfo() for details.
library(ggplot2)
## 0/0 packages newly attached/loaded, see sessionInfo() for details.
allalt = GRanges(rownames(assay(seg)))
allalt
## GRanges object with 27835 ranges and 0 metadata columns:
##           seqnames          ranges strand
##           <Rle>           <IRanges> <Rle>
##      [1]          1      12227-955755      *
##      [2]          1      957844-1139868      *
##      [3]          1     1140874-1471177      *
##      [4]          1     1475170-1855370      *
##      [5]          1     1857786-17257894      *
##      ...      ...      ...      ...
## [27831]         20      68410-1559342      *
## [27832]         20     1585705-1592359      *
## [27833]         20     1616247-62904955      *
## [27834]         21     9907492-48084286      *
## [27835]         22     16157938-51237572      *
## -----
## seqinfo: 22 sequences from an unspecified genome; no seqlengths
```

We'll focus on chromosome 17, where TP53 is found. Regions of genomic alteration are summarized to their midpoints.

```
g17 = allalt[seqnames(allalt)=="17"]
df17 = as(g17, "data.frame") # for ggplot2
df17$mid = .5*(df17$start+df17$end) # midpoint only
ggplot(df17, aes(x=mid)) + geom_density(bw=.2) + xlab("chr 17 bp")
```

This display shows a strong peak in the vicinity of 7.5 Mb on chromosome 17, near TP53.

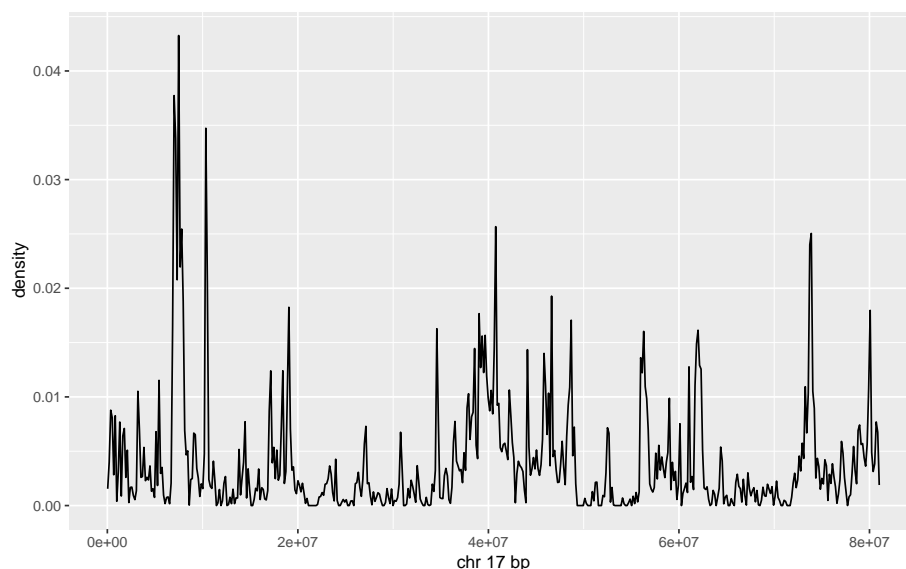


Figure 5: Density of recurrent genomic alterations on chromosome 17 for 48 angiosarcoma patients.

4 Genomic annotation resources relevant to cancer

4.1 Resources from UCSC, NCBI, and EMBL

Sequences for reference genome builds for human and other model organisms are supplied in BSgenome packages. BSgenome.Hsapiens.UCSC.hg19 provides all chromosomes and contigs for the 2009 build; the hg38 suffix may be used for the 2013 build. The recent “telomere to telomere” build is available as BSgenome.Hsapiens.NCBI.T2T.CHMv13v2.0.

NCBI's dbSNP catalog of genetic variants is provided in packages SNPlocs.Hsapiens.dbSNP[version].[reference]. For example, SNPlocs.Hsapiens.dbSNP155.GRCh38 includes position and nucleotide content information for over 1 billion rs numbers.

Tracks defined for the UCSC genome browser are also packaged. TxDb.Hsapiens.UCSC.knownGene.hg38 can be used to get gene, transcript, and exon location information for the hg38 build. The EnsDb packages provide similar information for annotations curated at EMBL.

```
library(EnsDb.Hsapiens.v86)
EnsDb.Hsapiens.v86
## EnsDb for Ensembl:
## |Backend: SQLite
## |Db type: EnsDb
## |Type of Gene ID: Ensembl Gene ID
## |Supporting package: ensembl
## |Db created by: ensembl package from Bioconductor
## |script_version: 0.3.0
## |Creation time: Thu May 18 16:32:27 2017
## |ensembl_version: 86
## |ensembl_host: localhost
## |Organism: homo_sapiens
## |taxonomy_id: 9606
```

```
## |genome_build: GRCh38
## |DBSCHEMAVERSION: 2.0
## | No. of genes: 63970.
## | No. of transcripts: 216741.
## |Protein data available.
```

The “genes” method provides addresses and additional annotations.

```
names(mcols(genes(EnsDb.Hsapiens.v86)))
## [1] "gene_id"          "gene_name"          "gene_biotype"        "seq_coord_system"
## [5] "symbol"           "entrezid"
head(table(genes(EnsDb.Hsapiens.v86)$gene_biotype))
##
##      3prime_overlapping_ncRNA      antisense
##              30              5703
## bidirectional_promoter_lncRNA      IG_C_gene
##              4              23
##      IG_C_pseudogene      IG_D_gene
##              11              64
```

More recent versions of Ensembl gene annotation are available from AnnotationHub, as illustrated above in section 2.5 with the creation of `ens110`.

4.2 Gene sets

Many methods have been developed to employ collections of genes for inference on hypotheses about cancer initiation or progression. The Molecular Signatures Database (MSigDB) is curated at Broad Institute, and can be harvested using the `msigdb` package.

Collect all gene sets for humans:

```
library(msigdb)
hssigs = getMsigdb(org="hs", id="SYM", version=getMsigdbVersions())
```

Find those with CANCER in their name:

```
nms = grep("CANCER", names(hssigs), value=TRUE)
head(nms)
## [1] "SOGA_COLORECTAL_CANCER_MYC_DN"
## [2] "SOGA_COLORECTAL_CANCER_MYC_UP"
## [3] "WATANABE_RECTAL_CANCER_RADIOOTHERAPY_RESPONSIVE_UP"
## [4] "LIU_PROSTATE_CANCER_UP"
## [5] "BERTUCCI_MEDULLARY_VS_DUCTAL_BREAST_CANCER_UP"
## [6] "WATANABE_COLON_CANCER_MSI_VS_MSS_UP"
wangmet = hssigs[["WANG_METASTASIS_OF_BREAST_CANCER_ESR1_UP"]]
wangmet
## setName: WANG_METASTASIS_OF_BREAST_CANCER_ESR1_UP
## geneIds: KPNA2, HDGFL3, ..., PSMC2 (total: 22)
## geneIdType: Symbol
## collectionType: Broad
## bcCategory: c2 (Curated)
## bcSubCategory: CGP
```

```
## details: use 'details(object)'
```

Information on provenance is bound together with the gene list:

```
details(wangmet)
## setName: WANG_METASTASIS_OF_BREAST_CANCER_ESR1_UP
## geneIds: KPNA2, HDGFL3, ..., PSMC2 (total: 22)
## geneIdType: Symbol
## collectionType: Broad
## bcCategory: c2 (Curated)
## bcSubCategory: CGP
## setIdentifier: LVY1HGGWMJ7:35020:Fri May 26 13:33:02 2023:1104005
## description: Genes whose expression in primary ER(+) [GeneID=2099] breast cancer tumors positively correlate
## (longDescription available)
## organism: Homo sapiens
## pubMedIds: 15721472
## urls: https://data.broadinstitute.org/gsea-msigdb/msigdb/release/2023.1.Hs/msigdb_v2023.1.Hs.xml.zip
## contributor: Arthur Liberzon
## setVersion: 2023.1
## creationDate:
```

4.3 Ontologies

Informal reasoning about cancer genomics employs conventional but frequently ambiguous terminology. In modern information science, ontologies are structured vocabularies (sets of “terms”, which may be single words or natural language phrases) accompanied by explicit statements of semantic relationships among terms.

Bioconductor provides several approaches for using ontologies in cancer data science. The most familiar ontology in this domain is Gene Ontology (GO), which organizes vocabulary about genes and gene products in the areas of molecular function, cellular components, and biological processes.

4.3.1 Ontology usage with AnnotationDbi

A common use case is to find genes or proteins associated with some biological process, component, or function. A phrase like ‘Golgi membrane’ can be found in Gene Ontology using the select method with GO.db:

```
library(GO.db)
select(GO.db, keytype="TERM",
       keys="Golgi membrane", columns=c("GOID", "DEFINITION", "ONTOLOGY"))
##          TERM          GOID
## 1 Golgi membrane GO:0000139
##
##                                     DEFINITION
## 1 The lipid bilayer surrounding any of the compartments of the Golgi apparatus.
##   ONTOLOGY
## 1      CC
```

Once the formal identifier is obtained, the org.Hs.eg.db package can be used to find mappings from the GO term to gene and protein identifiers. This generates a fairly large table:

```
library(org.Hs.eg.db)
go139 = select(org.Hs.eg.db, keys="G0:0000139", keytype="GO",
  columns=c("ENTREZID", "SYMBOL", "PFAM"))
dim(go139)
## [1] 1212    6
head(go139)
##           GO EVIDENCE ONTOLOGY ENTREZID SYMBOL  PFAM
## 1 G0:0000139      TAS      CC      28    ABO PF03414
## 2 G0:0000139      IEA      CC     102 ADAM10 PF00200
## 3 G0:0000139      IEA      CC     102 ADAM10 PF13574
## 4 G0:0000139      IEA      CC     102 ADAM10 PF01562
## 5 G0:0000139      TAS      CC     162 AP1B1 PF09066
## 6 G0:0000139      TAS      CC     162 AP1B1 PF01602
```

The evidence code TAS means that there is a “traceable author statement” associating the term of interest with the gene identified. The number of genes in traceable Golgi membrane:gene associations is found with

```
go139 |> dplyr::filter(EVIDENCE=="TAS") |> distinct(ENTREZID) |> count()
##           n
## 1    327
```

4.3.2 Ontology usage with rols

Access to a vast collection of ontologies is afforded by the EBI's Ontology Lookup Service (OLS). The rols package uses the OLS API to discover ontologic mapping of terms of interest. Here we'll consider the term “golgi membrane dynamics”, which is not found in GO. Again a multistep process is used.

```
library(rols)
lk1 = olsSearch(q="golgi membrane dynamics", exact=TRUE)
lk1
## Object of class 'OlsSearch':
##   query: golgi membrane dynamics
##   requested: 20 (out of 3)
##   response(s): 0
```

In this first step, we find how extensive is the response to the query. Certain searches yield tens of thousands of hits. With the exact parameter setting, the yield is modest. Now we extract a data.frame after requesting all records with `olsSearch`:

```
lk2 = olsSearch(lk1)
lk3 = as(lk2, "data.frame")
lk3$description = unlist(lk3$description)
kbl(lk3[,4:6], booktabs=TRUE) |> column_spec(2, width="15em") |> column_spec(3,
  width="15em")
```


short_form	description	label
NCIT_C119637	This gene is involved in both protein ubiquitination and Golgi membrane dynamics.	HACE1 Gene
NCIT_C119639	E3 ubiquitin-protein ligase HACE1 (909 aa, ~102 kDa) is encoded by the human HACE1 gene. This protein is involved in the regulation of both the ubiquitination and subsequent degradation of small GTPases, which modulates Golgi membrane dynamics.	E3 Ubiquitin-Protein Ligase HACE1
NCIT_C119638	Human HACE1 wild-type allele is located in the vicinity of 6q16.3 and is approximately 132 kb in length. This allele, which encodes E3 ubiquitin-protein ligase HACE1 protein, plays a role in the modulation of both Golgi membrane dynamics and ubiquitination. Mutations of the gene, including translocations that either reduce expression of the gene (t(6;15)(q21;q21)) or truncate the gene (t(5;6)(q21;q21)), are associated with Wilms tumor.	HACE1 wt Allele

The detailed descriptions of the NCI Thesaurus entries show the exact nature of the search outcome.

4.3.3 Cross-ontology relationships

Philosophically, ontology is the study of what there is. For applications in information science, boundaries need to be established so that ontological resources can be managed with well-defined scopes. In Gene Ontology, three sub-ontologies are explicitly identified for cellular components, biological processes, and molecular functions.

As knowledge of cell biology increases, the typology of cells becomes more and more intricate. Differentiation and definition of “cell types” involves concepts from immunology, protein science, anatomy, and other conceptual domains for which ontologies have been developed. Figure 6 presents, on the left, the hierarchy of cell type concepts starting at “lymphocyte”, leading to “Type II Natural Killer T cell secreting interferon gamma”. On the right, some of the GO and Protein Ontology (PR) cross-references in the Cell Ontology (CL) entry for the Type II NK cell are shown. The “cond” column of the table contains abbreviated tokens representing formal relationships linking the cell type to the protein or cellular component elements of PR and GO. The token “hasPMP” refers to the element of the Relation Ontology (RO) “has plasma membrane part” (RO:0002104).

Prospects for use of ontological discipline in the definition of new cell types are reviewed in a 2018 paper from the Venter Institute (Aevermann et al. (2018)). The field of biological ontology is rapidly advancing, and the integration of ontology search and inference with data analytic frameworks requires more effort at this time.

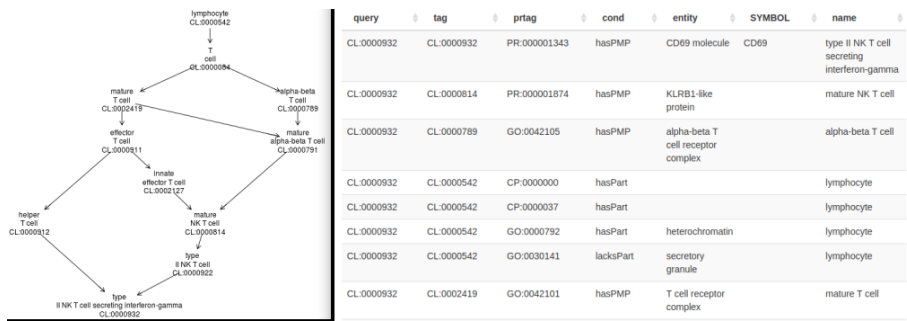


Figure 6: Ontology visualization and tabulation with ontoProc::ctmarks.

5 Analytical workflows

5.1 Overview

Table 5 presents an informal topical labeling for Bioconductor software packages with cancer mentioned in the Description field of package metadata.

Table 5: Topical organization of packages with cancer applications

topic	packages
Ancestry	RAIDS
Biomarkers	INDEED, iPath, RLassoCox
ceRNA	GDCRNATools
Clonal Evolution	CIMICE, LACE, OncoSimulR, TRONCO, CancerInSilico, cellscape
CNV	oncoscanR, SCOPE, ZygotityPredictor
DrugSensitivity	DepInfer, octad, PharmacoGx, rcellminer
Epigenetics	MethylMix, AMARETTO, COCOA, methylclock, missMethyl
HotSpots/Drivers/signatures	compSPOT, MoonlightR, Moonlight2R, DriverNet, genefu, mastR, pathifier, RESOLVE, macat, SigCheck, signeR, signifinder, supersigs, decompTumor2Sig, YAPSA
ImmuneModulation	easier
IsoformSwitching	IsoformSwitchAnalyzer
Literature mining	OncoScore
ncRNA	NoRCE
Radiomics	RadioGx
RecurrentFusion	copa, oppar
Spatial	SpatialDecon
SpecificCancers	consensusOV, PDATK, STROMA4
Splicing	OutSplice, psichomics
Subtyping	SCFA

The vignettes of each of these packages provide background and illustration of their roles in cancer genomics.

5.2 Packages supporting epigenomic analysis

Bioconductor also provides a diverse array of packages for analysis of epigenome data. Cancer is often studied under a developmental lens, so increasingly, studies are measuring cell states using epigenomic methods. Epigenomics is the study of chemical modifications and chromosomal conformations of DNA in a nucleus; in cancer epigenomics, we study how the cancer epigenome differs among cancers and how these relate to healthy epigenomes. As of 2023, Bioconductor includes 89 packages under *Epigenetics* and 93 packages tagged under *FunctionalGenomics*, including dozens of tools for analyzing a variety of epigenome assays, such as ATAC-seq, ChIP-seq, or bisulfite-seq. Among these are also tools that handle more general analysis, such as genomic region set enrichment.

First, for ATAC-seq data, bioconductor packages include general-purpose pipelines, including scPipe (Tian et al. 2018) and esATAC (Wei et al. 2018), which start from fastq files and produce feature count matrices. Alternatively, many practitioners elect to do general-purpose pipeline processing outside of R, and then bring the processed data into R for statistical analysis, visualization, and quality control. In this approach, ATACseqQC provides a variety of QC plots specific to ATAC-seq data (Ou et al. 2018).

For DNA methylation, many popular packages have been developed to help with all stages of a DNA methylation analysis. These include minfi [Aryee@2014], which specializes in methylation array analysis, biseq and bsseq (Hansen, Irizarry, and Wu 2012) which provide fundamental infrastructure for sequencing-based assays, and RnBeads (Müller et al. 2019), which provides a comprehensive general-purpose analysis of DNA methylation cohorts from arrays or sequencing-based assays. Other packages provide more specialized analysis approaches, such as MIRA (Lawson et al. 2018), which infers regulatory activity of transcription factors using DNA methylation signals, (Sheffield et al. 2018), or ELMER, which uses DNA methylation and gene expression in large cancer cohorts to infer transcription factor networks (Silva et al. 2018). EpiDISH infer the proportions of cell-types present in a bulk sample on the basis of DNA methylation data (Zheng et al. 2018).

Another popular epigenome experiment is ChIP-seq, and Bioconductor delivers many packages in this area. DiffBind (Stark and Brown 2011) is a popular approach for differential binding analysis of ChIP-seq peak data.

A variety of packages are also geared toward visualization of this type of data. GenomicDistributions (Kupkova et al. 2022) provides a variety of plots for visualization distributions of any type of genomic range data. The chromPlot package specializes in plots across chromosomes. Then, there are several packages that deal with unsupervised exploration of variation in epigenomic data. PathwayPCA, MOFA2 (Argelaguet et al. 2020) and COCOA (Lawson et al. 2020) can process any epigenomic signal data. A variety of alternative approaches for enrichment analysis, which include LOLA (Sheffield and Bock 2016), chipenrich, regionR (Gel et al. 2015), and FGNet (Aibar et al. 2015). Annotation packages are popular as well. ChIPpeakAnno (Zhu et al. 2010) and annotatr (Cavalcante and Sartor 2017) are popular packages for annotating genomic ranges.

5.3 Some details on prediction of responsiveness to immune checkpoint blockade

The National Cancer Institute website on checkpoint inhibitors in cancer immunotherapy (“Immune Checkpoint Inhibitors” [2022](#)) lists 12 different cancer types amenable to treatment via immune checkpoint inhibition. The “easier” package in Bioconductor assembles multiple systems biology resources to produce patient-specific prediction of responsiveness to immune checkpoint blockade (ICB), as described in Lapuente-Santana et al. ([2021](#)).

Figure 7 presents an overview of results of immune response assessment in a cohort of patients with bladder cancer reported in Mariathasan et al. ([2018](#)). Patient’s bulk RNA-seq data are used to develop multiple quantitative descriptors of the tumor microenvironment, and scores for processes regarded as hallmarks of anti-cancer immune responses.

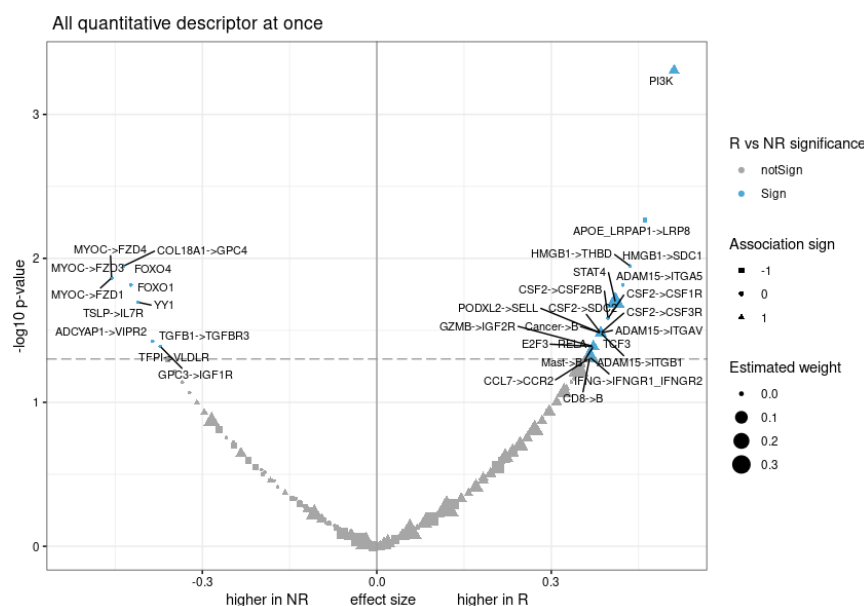


Figure 7: Comparison of genomic features distinguishing patients non-responsive and responsive to immune checkpoint blockade.

This display encapsulates a) the capacity of measurements of genomic elements to discriminate patients who respond to ICB for bladder cancer (position of labeled item on x axis), b) the direction of association of element activity with immune response (shape of glyph) and c) the relative magnitudes of weights (size of glyph) estimated for features in initial model fitting.

The design of this package is noteworthy in its approach to information hiding. Parameters estimated in machine learning of tissue-specific relations between quantitative descriptors of the tumor microenvironment and hallmarks of immune response are stored in ExperimentHub.

```
library(easierData)
list_easierData()
##      eh_id                                     title
## 1  EH6677 Mariathasan2018_PDL1_treatment
## 2  EH6678                                     opt_models
## 3  EH6679                                     opt_xtrain_stats
## 4  EH6680                                     TCGA_mean_pancancer
```

```
## 5 EH6681          TCGA_sd_pancancer
## 6 EH6682          cor_scores_genes
## 7 EH6683          intercell_networks
## 8 EH6684          lr_frequency_TCGA
## 9 EH6685          group_lrpairs
## 10 EH6686         HGNC_annotation
## 11 EH6687         scores_signature_genes
```

The structure of the stored model weights resource can be sketched by probing list elements.

```
mw = eh[["EH6678"]]
## see ?easierData and browseVignettes('easierData') for documentation
## loading from cache
names(mw) # TCGA tumor types
## [1] "LUAD" "LUSC" "BLCA" "BRCA" "CESC" "CRC" "GBM" "HNSC" "KIRC"
## [10] "KIRP" "LIHC" "OV" "PAAD" "PRAD" "SKCM" "STAD" "THCA" "UCEC"
## [19] "NSCLC"
names(mw[["LUAD"]]) # TME descriptors
## [1] "pathways" "immunecells" "tfs" "lrpairs" "ccpairs"
rownames(mw[["LUAD"]]$pathways$CYT) # predict cytolytic activity
## [1] "(Intercept)" "Androgen" "EGFR" "Estrogen" "Hypoxia"
## [6] "JAK-STAT" "MAPK" "NFKB" "p53" "PI3K"
## [11] "TGFb" "TNFa" "Trail" "VEGF" "WNT"
# using pathway activity
```

The vignette of the easier package steps through phases, using these tumor-type-specific weights to compute patient-specific measures of transcription factor activity or cell-cell interaction on the basis of bulk RNA-seq (units are transcripts per million), and a patient-specific measure of pathway activity using raw RNA-seq counts. These metrics may be of interest in their own right for applications other than establishing predictions of response to ICB.

Appendix 12 provides the names and versions of all packages used to produce this analysis.

5.4 Representing and visualizing a spatial transcriptomics experiment

```
library(SpatialFeatureExperiment)
library(SFEData)
jbr = JanesickBreastData("rep1")
jbr
## class: SpatialFeatureExperiment
## dim: 541 167782
## metadata(1): Samples
## assays(1): counts
## rownames(541): ABCC11 ACTA2 ... BLANK_0497 BLANK_0499
## rowData names(6): ID Symbol ... vars cv2
## colnames: NULL
## colData names(10): Sample Barcode ... nCounts nGenes
## reducedDimNames(0):
```

```
## mainExpName: NULL
## altExpNames(0):
## spatialCoords names(2) : x_centroid y_centroid
## imgData names(1): sample_id
##
## unit:
## Geometries:
## colGeometries: centroids (POINT), cellSeg (POLYGON), nucSeg (GEOMETRY)
##
## Graphs:
## sample01:
```

The expression values have strongly skewed distributions. For exploratory visualization we log-transform.

```
lfasn=log(as.numeric(assay(jbr["FASN",]))+1)
lpostn=log(as.numeric(assay(jbr["POSTN",]))+1)
```

Figure 8

```
strom = ggplot(colGeometries(jbr)$centroids, aes(colour=lpostn)) +
  geom_sf(size=.01) + scale_color_viridis_c() + ggtitle("POSTN, stromal")
fasn = ggplot(colGeometries(jbr)$centroids, aes(colour=lfasn)) +
  geom_sf(size=.01) + scale_color_viridis_c() + ggtitle("FASN, invasive")
library(gridExtra)
grid.arrange(strom, fasn, ncol=2)
```

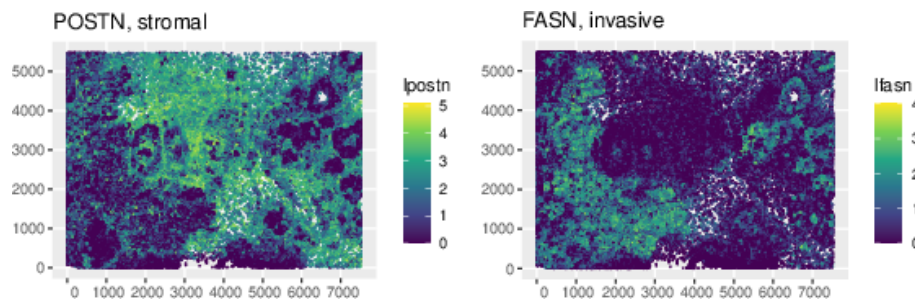


Figure 8: Informal rendering of data from Visium studies of breast cancer described in Janesick et al. 2023.

6 Components and processes for introducing new data, analytic tools, documents

6.1 Contributions and review

Proposed contributions to Bioconductor's ecosystem of software packages, data resources, and documentation are registered at <https://contributions.bioconductor.org/issues>. Contributors identify a public github.com repository that houses their software, or some durable open data repository for a data contribution. The contributor provides schematized information

on format, licensing, and commitment to maintenance of the contributed resource. After a series of automated and manual verification steps, the contributed resource enters the review process.

An example under review in December 2023 is the “methodical” package, submitted 27 September 2023. The issue number at the contributions site is 3169. This contribution is of particular interest as it addresses new data resources from whole genome and reduced representation bisulfite sequencing experiments. Specifics on these high-resolution studies of DNA methylation in a variety of clinical situations are given below.

6.2 Data structures

Inheritance is a key feature of object-oriented programming (OOP) that allows us to define a new class out of existing classes and add new features, which provides reusability of code. Inheritance carries over attributes and methods defined for base classes; ‘Attributes’ are variables that are bound in a class. They are used to define behavior and methods for objects of that class. ‘Methods’ are functions defined within a class that receive an instance of the class, conventionally called self, as the first argument. The attributes defined for a base class will automatically be present in the derived class, and the methods for the base class will work for the derived class. The R programming language has three different class systems: S3, S4, and Reference. Inheritance in S3 classes does not have any fixed definition, and hence attributes of S3 objects can be arbitrary. Derived classes, however, inherit the methods defined for the base class. Inheritance in S4 classes is more structured, and derived classes inherit both attributes and methods of the parent class. Reference classes are similar to S4 classes, but they are mutable and have reference semantics.

S4 classes are used extensively in Bioconductor to create data structures that store complex information, such as biological assay data and metadata, in one or more slots. The entire structure can then be assigned to an R object, and the types of information in each slot of the object are tightly controlled. S4 generics and methods define functions that can be applied to these objects, providing a rich software development infrastructure while ensuring interoperability, reusability, and efficiency.

Bioconductor have established Bioconductor classes to represent different types of biological data. Data and tools distributed through Bioconductor adopt Bioconductor classes, providing convenient methods and improving usability and interoperability within the Bioconductor ecosystem.

Data Types	Bioconductor Classes
Genomic coordinates (1-based, closed interval)	GRanges
Groups of genomic coordinates	GRangesList
Ragged genomic coordinates	RaggedExperiment
Gene sets	GeneSet
Rectangular Features x samples	SummarizedExperiment
Multi-omics data	MultiAssayExperiment
Single-cell data	SingleCellExperiment
Mass spectrometry data	Spectra

The `GRanges` class represents a collection of genomic ranges and associated annotations. Each element in the vector represents a set genomic ranges in terms of the sequence name (seqnames, typically the chromosome), start and end coordinates (ranges, as an `IRanges` object), strand (strand, either positive, negative, or unstranded), and optional metadata columns (e.g., `exon_id` and `exon_name` in the below).

```
GRanges object with 4 ranges and 2 metadata columns:
      seqnames      ranges strand |   exon_id   exon_name
      <Rle>        <IRanges> <Rle> | <integer> <character>
[1]      X 99883667-99884983     - |   667145 ENSE00001459322
[2]      X 99885756-99885863     - |   667146 ENSE00000868868
[3]      X 99887482-99887565     - |   667147 ENSE00000401072
[4]      X 99887538-99887565     - |   667148 ENSE00001849132
-----
seqinfo: 722 sequences (1 circular) from an unspecified genome
```

The `GRangesList` object serves as a container for genomic features consisting of multiple ranges that are grouped by a parent features, such as spliced transcripts that are comprised of exons. A `GRangesList` object behaves like a list and many of the same methods for `GRanges` objects are available for `GRangesList` object as well.

The `SummarizedExperiment` class (see Figure 1) is a matrix-like container, where rows represent features of interest (e.g., genes, transcripts, exons, etc.) and columns represent samples. The attributes of this object include experimental results (in assays), information on observations (in `rowData`) and samples (in `colData`), and additional metadata (in `metadata`). `SummarizedExperiment` objects can simultaneously manage several experimental results as long as they are of the same dimensions. The best benefit of using `SummarizedExperiment` class is the coordination of the metadata and assays when subsetting. `SummarizedExperiment` is similar to the historical `ExpressionSet` class, but more flexible in its row information, allowing both `GRanges` and `DataFrames`. `ExpressionSet` object can be easily converted to `SummarizedExperiment`.

`RangedSummarizedExperiment` inherits the `SummarizedExperiment` class, with the extended capability of storing genomic ranges (as a `GRanges` or `GRangesList` object) of interest instead of a `DataFrame` (`S4`-class objects similar to `data.frame`) of features in rows.

The `MultiAssayExperiment` class (presented above in Figure 2) is modeled after the `SummarizedExperiment` class. A `MultiAssayExperiment` instance `M` can be filtered as a three-dimensional array. When `G` is a vector of feature identifiers, `C` a vector of sample identifiers, and `E` a vector of experiment names, then `M[G, C, E]` is a `MultiAssayExperiment` with content restricted to the requested features, samples, and experiments. The `MultiAssayExperiment` package includes tooling to convert data content to “long” or “wide” formats. In long format, each element of the assay array occupies a row, accompanied by metadata associated with the element. In wide format, each sample occupies a row, accompanied by all associated assay and metadata elements.

6.3 Out-of-memory data representation strategies

We return to the “methodical” package submission mentioned above. A number of whole-genome bisulfite sequencing experiments on tumors from various anatomic sites are available in `ExperimentHub`. Metadata in that package shows that the datasets are large, ranging from 2-40 gigabytes. One smaller dataset is provided for illustration.


```
library(TumourMethData)
demm = download_meth_dataset("mcrpc-wgbs-hg38-chr11")
demm
## class: RangedSummarizedExperiment
## dim: 1333114 100
## metadata(5): genome is_h5 ref_CpG chrom_sizes descriptive_stats
## assays(2): beta cov
## rownames: NULL
## rowData names(0):
## colnames(100): DTB_003 DTB_005 ... DTB_265 DTB_266
## colData names(4): metastasis_site subtype age sex
rowRanges(demm)
## GRanges object with 1333114 ranges and 0 metadata columns:
##           seqnames      ranges strand
##           <Rle> <IRanges> <Rle>
##      [1]   chr11      60077      *
##      [2]   chr11      60088      *
##      [3]   chr11      60365      *
##      [4]   chr11      60941      *
##      [5]   chr11      60979      *
##      ...      ...      ...      ...
## [1333110] chr11 135076482      *
## [1333111] chr11 135076496      *
## [1333112] chr11 135076502      *
## [1333113] chr11 135076507      *
## [1333114] chr11 135076510      *
## -----
## seqinfo: 25 sequences from an unspecified genome; no seqlengths
names(colData(demm))
## [1] "metastasis_site" "subtype"      "age"      "sex"
table(demm$metastasis_site)
##
##      Bone      Liver Lymph_node      Other
##      43       11       38       8
```

References to `demm` involve an 800MB excerpt of a prostate cancer atlas with a storage footprint of 40GB. Ideally, queries about particular genomic regions on particular samples, whole-sample statistical summaries, and searches for patterns can be carried out without specific accommodation of the data size or representation. The `DelayedArray` package helps pursue this aim. We'll illustrate by interrogating the prostate cancer WGBS data for "beta" (fraction of locus that is methylated) values in the vicinity of gene `ATM`.

```
library(EnsDb.Hsapiens.v86)
gg = genes(EnsDb.Hsapiens.v86) # get gene addresses
atmpos = gg[gg$gene_name == "ATM" &
  gg$gene_biotype == "protein_coding"] # filter to ATM
seqlevelsStyle(atmpos) = "UCSC" # translate chr names
## Warning in (function (seqlevels, genome, new_style) : cannot switch some
## GRCh38's seqlevels from NCBI to UCSC style
assay(subsetByOverlaps(demm, atmpos+1e6)) # get betas
## <18110 x 100> DelayedMatrix object of type "double":
```

```
##          DTB_003  DTB_005  DTB_008  ...  DTB_265  DTB_266
##      [1,] 0.1052632 0.7659574 0.9206349 . 0.6944444 0.9411765
##      [2,] 0.4062500 0.9090909 0.9318182 . 0.5675676 1.0000000
##      [3,] 0.1379310 0.0000000 0.7400000 . 0.4642857 0.9230769
##      [4,] 0.2307692 0.9230769 0.9148936 . 0.8928571 0.9285714
##      [5,] 0.1481481 0.8500000 0.8863636 . 0.8709677 0.9761905
##      ...
## [18106,] 0.4137931 0.3142857 0.3207547 . 0.17647059 0.10000000
## [18107,] 0.2727273 0.2745098 0.4142857 . 0.22500000 0.32500000
## [18108,] 0.2258065 0.4800000 0.5774648 . 0.08888889 0.25000000
## [18109,] 0.5277778 0.7058824 0.8088235 . 0.55263158 0.97560976
## [18110,] 0.2777778 0.3137255 0.6956522 . 0.52631579 0.35714286
```

The numeric values presented above are just the “corners” of the associated array, presented as a “check” on the content requested. Transfer of array content to the CPU for numerical analysis only occurs on demand, which can be tailored to the quantity of RAM available at analysis time.

6.4 Quality assessment of Bioconductor resources

Figure 9 is an overview of the periodic ecosystem testing process for Bioconductor software packages in the release branch. All Bioconductor and CRAN packages on which they depend are present and are updated on change to sources.

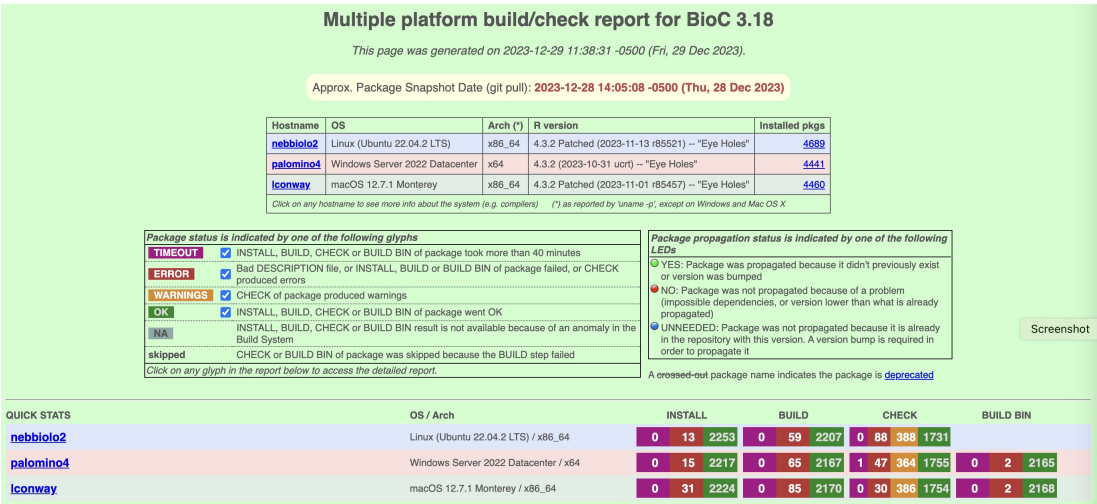


Figure 9: Build report for Bioc 3.18, 12-29-2023.

The project distributes source tarballs for Linux-like systems, and compiled binaries for MacOS and Windows. Numbers in red boxes indicate failures to install, build, or check. Failure events are frequently platform-specific; full logs are provided on the build report pages to help developers isolate and fix build and check errors. When failures are persistent, developers are contacted by core. If contact cannot be made and failures continue, packages are deprecated for at least one release, and then removed.

7 Pedagogics and workforce development

The Bioconductor project has undertaken a number of initiatives to support growth of the scientific workforce's capacity to efficiently integrate and interpret genome-scale experiments.

- **Partnering with The Carpentries.** The Carpentries <https://carpentries.org> is a non-profit organization focused on teaching programming and data science to researchers. The organization defines "good practices in lesson design and development, and open source collaboration skills". Bioconductor community members have created bioc-intro, bioc-project, and bioc-rnaseq repositories using The Carpentries Incubator template. This arrangement helps Bioconductor create and manage a "train the trainer" process according to tested pedagogical principles.
- **Curating monographs for topics in genomic data science.** The breadth of Bioconductor resources for genomics, combined with the energetic approach to software and annotation upkeep in the project, empowers Bioconductor developers to produce unified, wide-ranging, computable documents on topics of interest to the broader cancer genomics community. Books currently available at bioconductor.org include OSCA (Orchestrating Single Cell Analysis with Bioconductor), SingleRBook (Assigning cell types with SingleR), csawBook (Analysis of ChIP-seq data), OHCA (Orchestrating Hi-C Analysis with Bioconductor) and R for Mass Spectrometry. Very recently, Jacques Serizay of Institut Pasteur has contributed a book authoring framework called BiocBook. This transforms documents marked up in Posit's quarto format into web-based books backed up by Docker containers and maintained with templated GitHub actions. The OHCA book is produced and managed with BiocBook.
- **A system for authoring and deploying interactive workshops.**

Figure 10 gives an overview of the resources and objectives of the system underlying workshop.bioconductor.org. Given a kubernetes-enabled cluster the workshop system assembles

- compute and storage elements,
- static components (training texts and shareable data),
- development environments (containers with all runtime elements required to compile code, conduct analyses, communicate with GPUs).

A lightly customized deployment of the Galaxy system (usegalaxy.org) is used to deal with authentication and process initiation and termination.

This system has been used to serve interactive workshops in a number of international conferences. Content in R markdown or quarto can be produced by anyone interested in offering a workshop, and the "BiocWorkshopSubmit" app at workshop.bioconductor.org can be used to identify new content to the system. Markdown documents will be analyzed to determine what resources are needed for the containerization of workshop software and data components, and the container will be created and registered at the GitHub Container Registry. Arrangements to deploy the workshop over a given calendar period can be made with Bioconductor core. The workshop container can be used to conduct the workshop on any system with a Docker client.

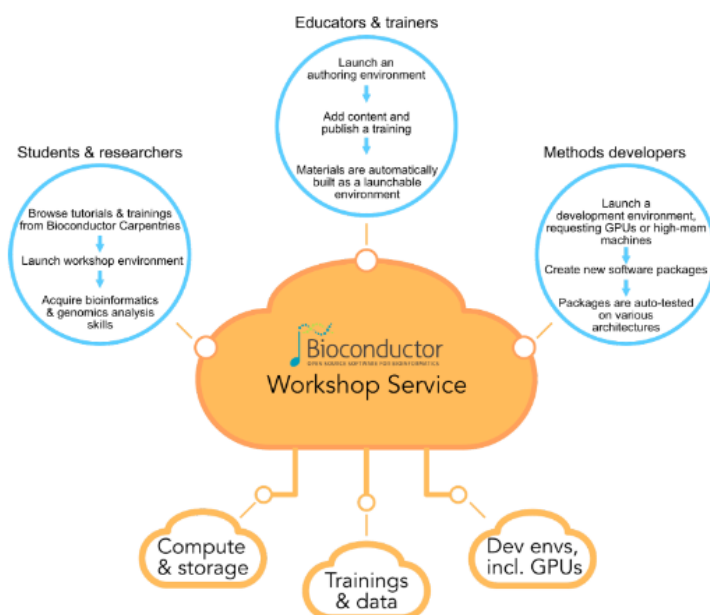


Figure 10: Workshop.bioconductor.org schematic.

8 Conclusions and paths forward

We have described several aspects of Bioconductor's approach to ecosystem management for cancer genomics data science resources. In light of the dynamism of biotechnological innovation, it is clear that the project must anticipate change. But it is challenging to introduce changes to processes on which a very large community depends for their daily research work. Commitments to supporting reproducible research entail that Bioconductor preserves decades worth of images of software and data for immediate retrieval via web request by parties unknown to the project.

We'll conclude this report with a few observations on general paths that the project is likely to take that should have favorable consequences to researchers in cancer genomics.

- **Language-agnostic data and annotation** The `alabaster.*` packages introduced in Bioconductor 3.17 are designed to convert existing Bioconductor data structures to formats that are more readily ingested by software in other languages. Thus the `alabaster.mae` package will convert a `MultiAssayExperiment` into a collection of files of metadata (serialized in JSON), sample-level data (serialized as CSV), and assay data (serialized to HDF5).
- **Zero-configuration genomic analysis environments** Users of Docker containers have long been able to take advantage of Bioconductor containers pre-populated with Rstudio and runtime resources to support installation of any desired software packages. The `bioc2u` system (<https://github.com/bioconductor/bioc2u>) in conjunction with `r2u` (<https://github.com/eddelbuettel/r2u>) introduces the availability of Debian packages for all Bioconductor packages, made available in a CRAN-like repository. Given a system running Ubuntu 22 or 20, the `apt` package manager will resolve any package requests with tested, fully linked binary packages. Users do not have to perform any configuration

or compilation of system utilities or package code. This practice can greatly reduce resource consumption that occurs when individuals or workflow systems need to compile every package and its dependencies to perform analyses.

- **Computation at the data** Several members of Bioconductor's development core are on the technical development team of NHGRI's Analysis and Visualization Laboratory (AnVIL). The aim of this project is to overthrow the prevalent model of downloading data for local analysis. AnVIL mobilizes commercial cloud computing and storage to support truly elastic genomic analysis – create and pay for only the computation you need. The basic strategy is described in Schatz et al. (2022). This system was used in the production of the Telomere-to-Telomere genome build, see Aganezov et al. (2022).

We hope that the project can continue to support researchers in cancer genomics for another 20 years!

9 Acknowledgments

This work was supported in part by NIH NCI 3U24CA180996-10S1, NHGRI 5U24HG004059-18, and NSF ACCESS allocation BIR190004.

10 Appendix 1 - Bioconductor software packages with 'cancer' in package description

Quoted text is the content of the Description element of the package DESCRIPTION. Names following the text are as reported in the Authors field.

package	desc
AMARETTO	"Integrating an increasing number of available multi-omics cancer data remains one of the main challenges to improve our understanding of cancer. One of the main challenges is using multi-omics data for identifying novel cancer driver genes. We have developed an algorithm, called AMARETTO, that integrates copy number, DNA methylation and gene expression data to identify a set of driver genes by analyzing cancer samples and connects them to clusters of co-expressed genes, which we define as modules. We applied AMARETTO in a pancancer setting to identify cancer driver genes and their modules on multiple cancer sites. AMARETTO captures modules enriched in angiogenesis, cell cycle and EMT, and modules that accurately predict survival and molecular subtypes. This allows AMARETTO to identify novel cancer driver genes directing canonical cancer pathways." –Jayendra Shinde, Celine Everaert, Shaimaa Bakr, Mohsen Nabian, Jishu Xu, Vincent Carey, Nathalie Pochet, Olivier Gevaert
BaalChIP	"The package offers functions to process multiple ChIP-seq BAM files and detect allele-specific events. Computes allele counts at individual variants (SNPs/SNVs), implements extensive QC steps to remove problematic variants, and utilizes a bayesian framework to identify statistically significant allele- specific events. BaalChIP is able to account for copy number differences between the two alleles, a known phenotypical feature of cancer samples." –Ines de Santiago, Wei Liu, Ke Yuan, Martin O'Reilly, Chandra SR Chilamakuri, Bruce Ponder, Kerstin Meyer, Florian Markowetz
bioCancer	"This package is a Shiny App to visualize and analyse interactively Multi-Assays of Cancer Genomic Data." –Karim Mezhoud
BiocOncoTK	"Provide a central interface to various tools for genome-scale analysis of cancer studies." –Vince Carey
biodbNci	"The biodbNci library is an extension of the biodb framework package. It provides access to biodbNci, a library for connecting to the National Cancer Institute (USA) CACTUS Database. It allows to retrieve entries by their accession number, and run specific web services." –Pierrick Roger

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canceR	"The package is user friendly interface based on the cgdscr and other modeling packages to explore, compare, and analyse all available Cancer Data (Clinical data, Gene Mutation, Gene Methylation, Gene Expression, Protein Phosphorylation, Copy Number Alteration) hosted by the Computational Biology Center at Memorial-Sloan-Kettering Cancer Center (MSKCC)." –Karim Mezhoud. Nuclear Safety & Security Department. Nuclear Science Center of Tunisia.
cbaf	"This package contains functions that allow analysing and comparing omic data across various cancers/cancer subgroups easily. So far, it is compatible with RNA-seq, microRNA-seq, microarray and methylation datasets that are stored on cbiportal.org." –Arman Shahrissa, Maryam Tahmasebi Birgani
cBioPortalData	"The cBioPortalData R package accesses study datasets from the cBio Cancer Genomics Portal. It accesses the data either from the pre-packaged zip / tar files or from the API interface that was recently implemented by the cBioPortal Data Team. The package can provide data in either tabular format or with MultiAssayExperiment object that uses familiar Bioconductor data representations." –Levi Waldron, Marcel Ramos, Karim Mezhoud
cbpManager	"This R package provides an R Shiny application that enables the user to generate, manage, and edit data and metadata files suitable for the import in cBioPortal for Cancer Genomics. Create cancer studies and edit its metadata. Upload mutation data of a patient that will be concatenated to the data_mutation_extended.txt file of the study. Create and edit clinical patient data, sample data, and timeline data. Create custom timeline tracks for patients." –Arsenij Ustjanzew, Federico Marini
ccfindR	"A collection of tools for cancer genomic data clustering analyses, including those for single cell RNA-seq. Cell clustering and feature gene selection analysis employ Bayesian (and maximum likelihood) non-negative matrix factorization (NMF) algorithm. Input data set consists of RNA count matrix, gene, and cell bar code annotations. Analysis outputs are factor matrices for multiple ranks and marginal likelihood values for each rank. The package includes utilities for downstream analyses, including meta-gene identification, visualization, and construction of rank-based trees for clusters." –Jun Woo, Jinhua Wang

cfDNAPro	"cfDNA fragments carry important features for building cancer sample classification ML models, such as fragment size, and fragment end motif etc. Analyzing and visualizing fragment size metrics, as well as other biological features in a curated, standardized, scalable, well-documented, and reproducible way might be time intensive. This package intends to resolve these problems and simplify the process. It offers two sets of functions for cfDNA feature characterization and visualization." –Haichao Wang, Hui Zhao, Elkie Chan, Christopher Smith, Tomer Kaplan, Florian Markowetz, Nitzan Rosenfeld
cfTools	"The cfTools R package provides methods for cell-free DNA (cfDNA) methylation data analysis to facilitate cfDNA-based studies. Given the methylation sequencing data of a cfDNA sample, for each cancer marker or tissue marker, we deconvolve the tumor-derived or tissue-specific reads from all reads falling in the marker region. Our read-based deconvolution algorithm exploits the pervasiveness of DNA methylation for signal enhancement, therefore can sensitively identify a trace amount of tumor-specific or tissue-specific cfDNA in plasma. cfTools provides functions for (1) cancer detection: sensitively detect tumor-derived cfDNA and estimate the tumor-derived cfDNA fraction (tumor burden); (2) tissue deconvolution: infer the tissue type composition and the cfDNA fraction of multiple tissue types for a plasma cfDNA sample. These functions can serve as foundations for more advanced cfDNA-based studies, including cancer diagnosis and disease monitoring." –Ran Hu, Mary Louisa Stackpole, Shuo Li, Xianghong Jasmine Zhou, Wenyuan Li
CIMICE	"CIMICE is a tool in the field of tumor phylogenetics and its goal is to build a Markov Chain (called Cancer Progression Markov Chain, CPMC) in order to model tumor subtypes evolution. The input of CIMICE is a Mutational Matrix, so a boolean matrix representing altered genes in a collection of samples. These samples are assumed to be obtained with single-cell DNA analysis techniques and the tool is specifically written to use the peculiarities of this data for the CMPC construction." –Nicolò Rossi

compSPOT	"Clonal cell groups share common mutations within cancer, precancer, and even clinically normal appearing tissues. The frequency and location of these mutations may predict prognosis and cancer risk. It has also been well established that certain genomic regions have increased sensitivity to acquiring mutations. Mutation-sensitive genomic regions may therefore serve as markers for predicting cancer risk. This package contains multiple functions to establish significantly mutated hotspots, compare hotspot mutation burden between samples, and perform exploratory data analysis of the correlation between hotspot mutation burden and personal risk factors for cancer, such as age, gender, and history of carcinogen exposure. This package allows users to identify robust genomic markers to help establish cancer risk." –Sydney Grant, Ella Sampson, Rhea Rodrigues, Gyorgy Paragh
consensusOV	"This package implements four major subtype classifiers for high-grade serous (HGS) ovarian cancer as described by Helland et al. (PLoS One, 2011), Bentink et al. (PLoS One, 2012), Verhaak et al. (J Clin Invest, 2013), and Konecny et al. (J Natl Cancer Inst, 2014). In addition, the package implements a consensus classifier, which consolidates and improves on the robustness of the proposed subtype classifiers, thereby providing reliable stratification of patients with HGS ovarian tumors of clearly defined subtype." –Gregory M Chen, Lavanya Kannan, Ludwig Geistlinger, Victor Kofia, Levi Waldron, Benjamin Haibe-Kains
copa	"COPA is a method to find genes that undergo recurrent fusion in a given cancer type by finding pairs of genes that have mutually exclusive outlier profiles." –James W. MacDonald
dce	"Compute differential causal effects (dce) on (biological) networks. Given observational samples from a control experiment and non-control (e.g., cancer) for two genes A and B, we can compute differential causal effects with a (generalized) linear regression. If the causal effect of gene A on gene B in the control samples is different from the causal effect in the non-control samples the dce will differ from zero. We regularize the dce computation by the inclusion of prior network information from pathway databases such as KEGG." –Kim Philipp Jablonski, Martin Pirkel

DeplInfeR	<p>"DeplInfeR integrates two experimentally accessible input data matrices: the drug sensitivity profiles of cancer cell lines or primary tumors ex-vivo (X), and the drug affinities of a set of proteins (Y), to infer a matrix of molecular protein dependencies of the cancers (β). DeplInfeR deconvolutes the protein inhibition effect on the viability phenotype by using regularized multivariate linear regression. It assigns a "dependence coefficient" to each protein and each sample, and therefore could be used to gain a causal and accurate understanding of functional consequences of genomic aberrations in a heterogeneous disease, as well as to guide the choice of pharmacological intervention for a specific cancer type, sub-type, or an individual patient. For more information, please read out preprint on bioRxiv: https://doi.org/10.1101/2022.01.11.475864." –Junyan Lu, Alina Batzilla</p>
DriverNet	<p>"DriverNet is a package to predict functional important driver genes in cancer by integrating genome data (mutation and copy number variation data) and transcriptome data (gene expression data). The different kinds of data are combined by an influence graph, which is a gene-gene interaction network deduced from pathway data. A greedy algorithm is used to find the possible driver genes, which may mutated in a larger number of patients and these mutations will push the gene expression values of the connected genes to some extreme values." –Ali Bashashati, Reza Haffari, Jiarui Ding, Gavin Ha, Kenneth Liu, Jamie Rosner, Sohrab Shah</p>
easier	<p>"This package provides a workflow for the use of EaSlER tool, developed to assess patients' likelihood to respond to ICB therapies providing just the patients' RNA-seq data as input. We integrate RNA-seq data with different types of prior knowledge to extract quantitative descriptors of the tumor microenvironment from several points of view, including composition of the immune repertoire, and activity of intra- and extra-cellular communications. Then, we use multi-task machine learning trained in TCGA data to identify how these descriptors can simultaneously predict several state-of-the-art hallmarks of anti-cancer immune response. In this way we derive cancer-specific models and identify cancer-specific systems biomarkers of immune response. These biomarkers have been experimentally validated in the literature and the performance of EaSlER predictions has been validated using independent datasets from four different cancer types with patients treated with anti-PD1 or anti-PDL1 therapy." –Oscar Lapuente-Santana, Federico Marini, Arsenij Ustjanzew, Francesca Finotello, Federica Eduati</p>

GDCRNATools	<p>"This is an easy-to-use package for downloading, organizing, and integrative analyzing RNA expression data in GDC with an emphasis on deciphering the lncRNA-mRNA related ceRNA regulatory network in cancer. Three databases of lncRNA-miRNA interactions including spongeScan, starBase, and miRcode, as well as three databases of mRNA-miRNA interactions including miRTarBase, starBase, and miRcode are incorporated into the package for ceRNAs network construction. limma, edgeR, and DESeq2 can be used to identify differentially expressed genes/miRNAs. Functional enrichment analyses including GO, KEGG, and DO can be performed based on the clusterProfiler and DO packages. Both univariate CoxPH and KM survival analyses of multiple genes can be implemented in the package. Besides some routine visualization functions such as volcano plot, bar plot, and KM plot, a few simply shiny apps are developed to facilitate visualization of results on a local webpage."</p> <p>—Ruidong Li, Han Qu, Shibo Wang, Julong Wei, Le Zhang, Renyuan Ma, Jianming Lu, Jianguo Zhu, Wei-De Zhong, Zhenyu Jia</p>
genefu	<p>"This package contains functions implementing various tasks usually required by gene expression analysis, especially in breast cancer studies: gene mapping between different microarray platforms, identification of molecular subtypes, implementation of published gene signatures, gene selection, and survival analysis." —Deena M.A. Gendoo, Natchar Ratanasirigulchai, Markus S. Schroeder, Laia Pare, Joel S Parker, Aleix Prat, Nikta Feizi, Christopher Eeles, Benjamin Haibe-Kains</p>
GeoTcgaData	<p>"Gene Expression Omnibus(GEO) and The Cancer Genome Atlas (TCGA) provide us with a wealth of data, such as RNA-seq, DNA Methylation, SNP and Copy number variation data. It's easy to download data from TCGA using the gdc tool, but processing these data into a format suitable for bioinformatics analysis requires more work. This R package was developed to handle these data." —Erqiang Hu</p>
INDEED	<p>"An R package for integrated differential expression and differential network analysis based on omic data for cancer biomarker discovery. Both correlation and partial correlation can be used to generate differential network to aid the traditional differential expression analysis to identify changes between biomolecules on both their expression and pairwise association levels. A detailed description of the methodology has been published in Methods journal (PMID: 27592383). An interactive visualization feature allows for the exploration and selection of candidate biomarkers." —Yiming Zuo, Kian Ghaffari, Zhenzhi Li</p>

iPath	"iPath is the Bioconductor package used for calculating personalized pathway score and test the association with survival outcomes. Abundant single-gene biomarkers have been identified and used in the clinics. However, hundreds of oncogenes or tumor-suppressor genes are involved during the process of tumorigenesis. We believe individual-level expression patterns of pre-defined pathways or gene sets are better biomarkers than single genes. In this study, we devised a computational method named iPath to identify prognostic biomarker pathways, one sample at a time. To test its utility, we conducted a pan-cancer analysis across 14 cancer types from The Cancer Genome Atlas and demonstrated that iPath is capable of identifying highly predictive biomarkers for clinical outcomes, including overall survival, tumor subtypes, and tumor stage classifications. We found that pathway-based biomarkers are more robust and effective than single genes." –Kenong Su, Zhaohui Qin
LACE	"LACE is an algorithmic framework that processes single-cell somatic mutation profiles from cancer samples collected at different time points and in distinct experimental settings, to produce longitudinal models of cancer evolution. The approach solves a Boolean Matrix Factorization problem with phylogenetic constraints, by maximizing a weighed likelihood function computed on multiple time points." –Daniele Ramazzotti, Fabrizio Angaroni, Davide Maspero, Alex Graudenzi, Luca De Sano, Gianluca Ascolani
macat	"This library contains functions to investigate links between differential gene expression and the chromosomal localization of the genes. MACAT is motivated by the common observation of phenomena involving large chromosomal regions in tumor cells. MACAT is the implementation of a statistical approach for identifying significantly differentially expressed chromosome regions. The functions have been tested on a publicly available data set about acute lymphoblastic leukemia (Yeoh et al.Cancer Cell 2002), which is provided in the library 'stjudem'." –Benjamin Georgi, Matthias Heinig, Stefan Roepcke, Sebastian Schmeier, Joern Toedling
maftools	"Analyze and visualize Mutation Annotation Format (MAF) files from large scale sequencing studies. This package provides various functions to perform most commonly used analyses in cancer genomics and to create feature rich customizable visualizations with minimal effort." –Anand Mayakonda

mastR	"mastR is an R package designed for automated screening of signatures of interest for specific research questions. The package is developed for generating refined lists of signature genes from multiple group comparisons based on the results from edgeR and limma differential expression (DE) analysis workflow. It also takes into account the background noise of tissue-specificity, which is often ignored by other marker generation tools. This package is particularly useful for the identification of group markers in various biological and medical applications, including cancer research and developmental biology." –Jinjin Chen, Ahmed Mohamed, Chin Wee Tan
MethylMix	"MethylMix is an algorithm implemented to identify hyper and hypomethylated genes for a disease. MethylMix is based on a beta mixture model to identify methylation states and compares them with the normal DNA methylation state. MethylMix uses a novel statistic, the Differential Methylation value or DM-value defined as the difference of a methylation state with the normal methylation state. Finally, matched gene expression data is used to identify, besides differential, functional methylation states by focusing on methylation changes that effect gene expression. References: Gevaert O. MethylMix: an R package for identifying DNA methylation-driven genes. <i>Bioinformatics</i> (Oxford, England). 2015;31(11):1839-41. doi:10.1093/bioinformatics/btv020. Gevaert O, Tibshirani R, Plevritis SK. Pancancer analysis of DNA methylation-driven genes using MethylMix. <i>Genome Biology</i> . 2015;16(1):17. doi:10.1186/s13059-014-0579-8." –Olivier Gevaert

Moonlight2R

"The understanding of cancer mechanism requires the identification of genes playing a role in the development of the pathology and the characterization of their role (notably oncogenes and tumor suppressors). We present an updated version of the R/bioconductor package called MoonlightR, namely Moonlight2R, which returns a list of candidate driver genes for specific cancer types on the basis of omics data integration. The Moonlight framework contains a primary layer where gene expression data and information about biological processes are integrated to predict genes called oncogenic mediators, divided into putative tumor suppressors and putative oncogenes. This is done through functional enrichment analyses, gene regulatory networks and upstream regulator analyses to score the importance of well-known biological processes with respect to the studied cancer type. By evaluating the effect of the oncogenic mediators on biological processes or through random forests, the primary layer predicts two putative roles for the oncogenic mediators: i) tumor suppressor genes (TSGs) and ii) oncogenes (OCGs). As gene expression data alone is not enough to explain the deregulation of the genes, a second layer of evidence is needed. We have automated the integration of a secondary mutational layer through new functionalities in Moonlight2R. These functionalities analyze mutations in the cancer cohort and classifies these into driver and passenger mutations using the driver mutation prediction tool, CScape-somatic. Those oncogenic mediators with at least one driver mutation are retained as the driver genes. As a consequence, this methodology does not only identify genes playing a dual role (e.g. TSG in one cancer type and OCG in another) but also helps in elucidating the biological processes underlying their specific roles. In particular, Moonlight2R can be used to discover OCGs and TSGs in the same cancer type. This may for instance help in answering the question whether some genes change role between early stages (I, II) and late stages (III, IV). In the future, this analysis could be useful to determine the causes of different resistances to chemotherapeutic treatments." –Mona Nourbakhsh, Astrid Saksager, Nikola Tom, Xi Steven Chen, Antonio Colaprico, Catharina Olsen, Matteo Tiberti, Elena Papaleo

MoonlightR

"Motivation: The understanding of cancer mechanism requires the identification of genes playing a role in the development of the pathology and the characterization of their role (notably oncogenes and tumor suppressors). Results: We present an R/bioconductor package called MoonlightR which returns a list of candidate driver genes for specific cancer types on the basis of TCGA expression data. The method first infers gene regulatory networks and then carries out a functional enrichment analysis (FEA) (implementing an upstream regulator analysis, URA) to score the importance of well-known biological processes with respect to the studied cancer type. Eventually, by means of random forests, MoonlightR predicts two specific roles for the candidate driver genes: i) tumor suppressor genes (TSGs) and ii) oncogenes (OCGs). As a consequence, this methodology does not only identify genes playing a dual role (e.g. TSG in one cancer type and OCG in another) but also helps in elucidating the biological processes underlying their specific roles. In particular, MoonlightR can be used to discover OCGs and TSGs in the same cancer type. This may help in answering the question whether some genes change role between early stages (I, II) and late stages (III, IV) in breast cancer. In the future, this analysis could be useful to determine the causes of different resistances to chemotherapeutic treatments." –Antonio Colaprico, Catharina Olsen, Matthew H. Bailey, Gabriel J. Odom, Thilde Terkelsen, Mona Nourbakhsh, Astrid Saksager, Tiago C. Silva, André V. Olsen, Laura Cantini, Andrei Zinovyev, Emmanuel Barillot, Houtan Noushmehr, Gloria Bertoli, Isabella Castiglioni, Claudia Cava, Gianluca Bontempi, Xi Steven Chen, Elena Papaleo, Matteo Tiberti

NoRCE	<p>"While some non-coding RNAs (ncRNAs) are assigned critical regulatory roles, most remain functionally uncharacterized. This presents a challenge whenever an interesting set of ncRNAs needs to be analyzed in a functional context. Transcripts located close-by on the genome are often regulated together. This genomic proximity on the sequence can hint to a functional association. We present a tool, NoRCE, that performs cis enrichment analysis for a given set of ncRNAs. Enrichment is carried out using the functional annotations of the coding genes located proximal to the input ncRNAs. Other biologically relevant information such as topologically associating domain (TAD) boundaries, co-expression patterns, and miRNA target prediction information can be incorporated to conduct a richer enrichment analysis. To this end, NoRCE includes several relevant datasets as part of its data repository, including cell-line specific TAD boundaries, functional gene sets, and expression data for coding & ncRNAs specific to cancer. Additionally, the users can utilize custom data files in their investigation. Enrichment results can be retrieved in a tabular format or visualized in several different ways. NoRCE is currently available for the following species: human, mouse, rat, zebrafish, fruit fly, worm, and yeast." –Gulden Olgun</p>
octad	<p>"OCTAD provides a platform for virtually screening compounds targeting precise cancer patient groups. The essential idea is to identify drugs that reverse the gene expression signature of disease by tamping down over-expressed genes and stimulating weakly expressed ones. The package offers deep-learning based reference tissue selection, disease gene expression signature creation, pathway enrichment analysis, drug reversal potency scoring, cancer cell line selection, drug enrichment analysis and in silico hit validation. It currently covers ~20,000 patient tissue samples covering 50 cancer types, and expression profiles for ~12,000 distinct compounds." –E. Chekalin, S. Paithankar, B. Zeng, B. Glicksberg, P. Newbury, J. Xing, K. Liu, A. Wen, D. Joseph, B. Chen</p>
oncoscanR	<p>"The software uses the copy number segments from a text file and identifies all chromosome arms that are globally altered and computes various genome-wide scores. The following HRD scores (characteristic of BRCA-mutated cancers) are included: LST, HR-LOH, nLST and gLOH. the package is tailored for the ThermoFisher Oncoscan assay analyzed with their Chromosome Alteration Suite (ChAS) but can be adapted to any input." –Yann Christinat, Geneva University Hospitals</p>

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OncoScore	"OncoScore is a tool to measure the association of genes to cancer based on citation frequencies in biomedical literature. The score is evaluated from PubMed literature by dynamically updatable web queries." –Luca De Sano, Carlo Gambacorti Passerini, Rocco Piazza, Daniele Ramazzotti, Roberta Spinelli
OncoSimulR	"Functions for forward population genetic simulation in asexual populations, with special focus on cancer progression. Fitness can be an arbitrary function of genetic interactions between multiple genes or modules of genes, including epistasis, order restrictions in mutation accumulation, and order effects. Fitness (including just birth, just death, or both birth and death) can also be a function of the relative and absolute frequencies of other genotypes (i.e., frequency-dependent fitness). Mutation rates can differ between genes, and we can include mutator/antimutator genes (to model mutator phenotypes). Simulating multi-species scenarios and therapeutic interventions, including adaptive therapy, is also possible. Simulations use continuous-time models and can include driver and passenger genes and modules. Also included are functions for: simulating random DAGs of the type found in Oncogenetic Trees, Conjunctive Bayesian Networks, and other cancer progression models; plotting and sampling from single or multiple realizations of the simulations, including single-cell sampling; plotting the parent-child relationships of the clones; generating random fitness landscapes (Rough Mount Fuji, House of Cards, additive, NK, Ising, and Eggbox models) and plotting them." –Ramon Diaz-Uriarte, Sergio Sanchez-Carrillo, Juan Antonio Miguel Gonzalez, Alberto Gonzalez Klein, Javier Muñoz Haro, Javier Lopez Cano, Niklas Endres, Mark Taylor, Arash Partow, Sophie Brouillet, Sebastian Matuszewski, Harry Annoni, Luca Ferretti, Guillaume Achaz, Tymoteusz Wolodzko, Guillermo Gorines Cordero, Ivan Lorca Alonso, Francisco Muñoz Lopez, David Roncero Moro, Alvaro Quevedo, Pablo Perez, Cristina Devesa, Alejandro Herrador, Holger Froehlich, Florian Markowetz, Achim Tresch, Theresa Niederberger, Christian Bender, Matthias Maneck, Claudio Lottaz, Tim Beissbarth, Sara Dorado Alfaro, Miguel Hernandez del Valle, Alvaro Huertas Garcia, Diego Mananes Cayero, Alejandro Martin Muñoz, Marta Couce Iglesias, Silvia Garcia Cobos, Carlos Madariaga Aramendi, Ana Rodriguez Ronchel, Lucia Sanchez Garcia, Yolanda Benitez Quesada, Asier Fernandez Pato, Esperanza Lopez Lopez, Alberto Manuel Parra Perez, Jorge Garcia Calleja, Ana del Ramo Galian, Alejandro de los Reyes Benitez, Guillermo Garcia Hoyos, Rosalia Palomino Cabrera, Rafael Barrero Rodriguez, Silvia Talavera Marcos

oppar	"The R implementation of mCOPA package published by Wang et al. (2012). Oppar provides methods for Cancer Outlier profile Analysis. Although initially developed to detect outlier genes in cancer studies, methods presented in oppar can be used for outlier profile analysis in general. In addition, tools are provided for gene set enrichment and pathway analysis." –Chenwei Wang, Alperen Taciroglu, Stefan R Maetschke, Colleen C Nelson, Mark Ragan, Melissa Davis, Soroor Hediye zadeh, Momeneh Foroutan
ORFhunterR	"The ORFhunterR package is a R and C++ library for an automatic determination and annotation of open reading frames (ORF) in a large set of RNA molecules. It efficiently implements the machine learning model based on vectorization of nucleotide sequences and the random forest classification algorithm. The ORFhunterR package consists of a set of functions written in the R language in conjunction with C++. The efficiency of the package was confirmed by the examples of the analysis of RNA molecules from the NCBI RefSeq and Ensembl databases. The package can be used in basic and applied biomedical research related to the study of the transcriptome of normal as well as altered (for example, cancer) human cells." –Vasily V. Grinev, Mikalai M. Yatskou, Victor V. Skakun, Maryna Chepeleva, Petr V. Nazarov
OutSplice	"An easy to use tool that can compare splicing events in tumor and normal tissue samples using either a user generated matrix, or data from The Cancer Genome Atlas (TCGA). This package generates a matrix of splicing outliers that are significantly over or underexpressed in tumors samples compared to normal denoted by chromosome location. The package also will calculate the splicing burden in each tumor and characterize the types of splicing events that occur." –Joseph Bendik, Sandhya Kalavacherla, Michael Considine, Bahman Afsari, Michael F. Ochs, Joseph Califano, Daria A. Gaykalova, Elana Fertig, Theresa Guo
pathifier	"Pathifier is an algorithm that infers pathway deregulation scores for each tumor sample on the basis of expression data. This score is determined, in a context-specific manner, for every particular dataset and type of cancer that is being investigated. The algorithm transforms gene-level information into pathway-level information, generating a compact and biologically relevant representation of each sample." –Yotam Drier

paxtoolsr	"The package provides a set of R functions for interacting with BioPAX OWL files using Paxtools and the querying Pathway Commons (PC) molecular interaction database. Pathway Commons is a project by the Memorial Sloan-Kettering Cancer Center (MSKCC), Dana-Farber Cancer Institute (DFCI), and the University of Toronto. Pathway Commons databases include: BIND, BioGRID, CORUM, CTD, DIP, DrugBank, HPRD, HumanCyc, IntAct, KEGG, MirTarBase, Panther, PhosphoSitePlus, Reactome, RECON, TRANSFAC." –Augustin Luna
PDATK	"Pancreatic ductal adenocarcinoma (PDA) has a relatively poor prognosis and is one of the most lethal cancers. Molecular classification of gene expression profiles holds the potential to identify meaningful subtypes which can inform therapeutic strategy in the clinical setting. The Pancreatic Cancer Adenocarcinoma Tool-Kit (PDATK) provides an S4 class-based interface for performing unsupervised subtype discovery, cross-cohort meta-clustering, gene-expression-based classification, and subsequent survival analysis to identify prognostically useful subtypes in pancreatic cancer and beyond. Two novel methods, Consensus Subtypes in Pancreatic Cancer (CSPC) and Pancreatic Cancer Overall Survival Predictor (PCOSP) are included for consensus-based meta-clustering and overall-survival prediction, respectively. Additionally, four published subtype classifiers and three published prognostic gene signatures are included to allow users to easily recreate published results, apply existing classifiers to new data, and benchmark the relative performance of new methods. The use of existing Bioconductor classes as input to all PDATK classes and methods enables integration with existing Bioconductor datasets, including the 21 pancreatic cancer patient cohorts available in the MetaGxPancreas data package. PDATK has been used to replicate results from Sandhu et al (2019) [https://doi.org/10.1200/cci.18.00102] and an additional paper is in the works using CSPC to validate subtypes from the included published classifiers, both of which use the data available in MetaGxPancreas. The inclusion of subtype centroids and prognostic gene signatures from these and other publications will enable researchers and clinicians to classify novel patient gene expression data, allowing the direct clinical application of the classifiers included in PDATK. Overall, PDATK provides a rich set of tools to identify and validate useful prognostic and molecular subtypes based on gene-expression data, benchmark new classifiers against existing ones, and apply discovered classifiers on novel patient data to inform clinical decision making." –Vandana Sandhu, Heewon Seo, Christopher Eeles, Neha Rohatgi, Benjamin Haibe-Kains

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PharmacoGx	"Contains a set of functions to perform large-scale analysis of pharmaco-genomic data. These include the PharmacoSet object for storing the results of pharmacogenomic experiments, as well as a number of functions for computing common summaries of drug-dose response and correlating them with the molecular features in a cancer cell-line." –Petr Smirnov, Christopher Eeles, Zhaleh Safikhani, Mark Freeman, Feifei Li, Jeremiah Joseph, Benjamin Haibe-Kains
psichomics	"Interactive R package with an intuitive Shiny-based graphical interface for alternative splicing quantification and integrative analyses of alternative splicing and gene expression based on The Cancer Genome Atlas (TCGA), the Genotype-Tissue Expression project (GTEx), Sequence Read Archive (SRA) and user-provided data. The tool interactively performs survival, dimensionality reduction and median- and variance-based differential splicing and gene expression analyses that benefit from the incorporation of clinical and molecular sample-associated features (such as tumour stage or survival). Interactive visual access to genomic mapping and functional annotation of selected alternative splicing events is also included." –Nuno Saraiva-Agostinho, Nuno Luís Barbosa-Morais, André Falcão, Lina Gallego Paez, Marie Bordone, Teresa Maia, Mariana Ferreira, Ana Carolina Leote, Bernardo de Almeida
RadioGx	"Computational tool box for radio-genomic analysis which integrates radio-response data, radio-biological modelling and comprehensive cell line annotations for hundreds of cancer cell lines. The 'RadioSet' class enables creation and manipulation of standardized datasets including information about cancer cells lines, radio-response assays and dose-response indicators. Included methods allow fitting and plotting dose-response data using established radio-biological models along with quality control to validate results. Additional functions related to fitting and plotting dose response curves, quantifying statistical correlation and calculating area under the curve (AUC) or survival fraction (SF) are included. For more details please see the included documentation, references, as well as: Manem, V. et al (2018) <doi:10.1101/449793>." –Venkata Manem, Petr Smirnov, Ian Smith, Meghan Lambie, Christopher Eeles, Scott Bratman, Jeremiah Joseph, Benjamin Haibe-Kains

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RAIDS	"This package implements specialized algorithms that enable genetic ancestry inference from various cancer sequences sources (RNA, Exome and Whole-Genome sequences). This package also implements a simulation algorithm that generates synthetic cancer-derived data. This code and analysis pipeline was designed and developed for the following publication: Belleau, P et al. Genetic Ancestry Inference from Cancer-Derived Molecular Data across Genomic and Transcriptomic Platforms. Cancer Res 1 January 2023; 83 (1): 49–58." –Pascal Belleau, Astrid Deschênes, David A. Tuveson, Alexander Krasnitz
rCellMiner	"The NCI-60 cancer cell line panel has been used over the course of several decades as an anti-cancer drug screen. This panel was developed as part of the Developmental Therapeutics Program (DTP, http://dtp.nci.nih.gov/) of the U.S. National Cancer Institute (NCI). Thousands of compounds have been tested on the NCI-60, which have been extensively characterized by many platforms for gene and protein expression, copy number, mutation, and others (Reinhold, et al., 2012). The purpose of the CellMiner project (http://discover.nci.nih.gov/cellminer) has been to integrate data from multiple platforms used to analyze the NCI-60 and to provide a powerful suite of tools for exploration of NCI-60 data." –Augustin Luna, Vinodh Rajapakse, Fabricio Sousa
RESOLVE	"Cancer is a genetic disease caused by somatic mutations in genes controlling key biological functions such as cellular growth and division. Such mutations may arise both through cell-intrinsic and exogenous processes, generating characteristic mutational patterns over the genome named mutational signatures. The study of mutational signatures have become a standard component of modern genomics studies, since it can reveal which (environmental and endogenous) mutagenic processes are active in a tumor, and may highlight markers for therapeutic response. Mutational signatures computational analysis presents many pitfalls. First, the task of determining the number of signatures is very complex and depends on heuristics. Second, several signatures have no clear etiology, casting doubt on them being computational artifacts rather than due to mutagenic processes. Last, approaches for signatures assignment are greatly influenced by the set of signatures used for the analysis. To overcome these limitations, we developed RESOLVE (Robust ESTimation Of mutational signatures Via rEgularization), a framework that allows the efficient extraction and assignment of mutational signatures. RESOLVE implements a novel algorithm that enables (i) the efficient extraction, (ii) exposure estimation, and (iii) confidence assessment during the computational inference of mutational signatures." –Daniele Ramazzotti, Luca De Sano

RLassoCox	"RLassoCox is a package that implements the RLasso-Cox model proposed by Wei Liu. The RLasso-Cox model integrates gene interaction information into the Lasso-Cox model for accurate survival prediction and survival biomarker discovery. It is based on the hypothesis that topologically important genes in the gene interaction network tend to have stable expression changes. The RLasso-Cox model uses random walk to evaluate the topological weight of genes, and then highlights topologically important genes to improve the generalization ability of the Lasso-Cox model. The RLasso-Cox model has the advantage of identifying small gene sets with high prognostic performance on independent datasets, which may play an important role in identifying robust survival biomarkers for various cancer types." –Wei Liu
RTCGA	"The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA. It contains clinical information, genomic characterization data, and high level sequence analysis of the tumor genomes. The key is to understand genomics to improve cancer care. RTCGA package offers download and integration of the variety and volume of TCGA data using patient barcode key, what enables easier data possession. This may have an beneficial influence on impact on development of science and improvement of patients' treatment. Furthermore, RTCGA package transforms TCGA data to tidy form which is convenient to use." –Marcin Kosinski, Przemyslaw Biecek, Witold Chodor
RTCGAToolbox	"Managing data from large scale projects such as The Cancer Genome Atlas (TCGA) for further analysis is an important and time consuming step for research projects. Several efforts, such as Firehose project, make TCGA pre-processed data publicly available via web services and data portals but it requires managing, downloading and preparing the data for following steps. We developed an open source and extensible R based data client for Firehose pre-processed data and demonstrated its use with sample case studies. Results showed that RTCGAToolbox could improve data management for researchers who are interested with TCGA data. In addition, it can be integrated with other analysis pipelines for following data analysis." –Mehmet Samur, Marcel Ramos, Ludwig Geistlinger
SCFA	"Subtyping via Consensus Factor Analysis (SCFA) can efficiently remove noisy signals from consistent molecular patterns in multi-omics data. SCFA first uses an autoencoder to select only important features and then repeatedly performs factor analysis to represent the data with different numbers of factors. Using these representations, it can reliably identify cancer subtypes and accurately predict risk scores of patients." –Duc Tran, Hung Nguyen, Tin Nguyen

SCOPE	"Whole genome single-cell DNA sequencing (scDNA-seq) enables characterization of copy number profiles at the cellular level. This circumvents the averaging effects associated with bulk-tissue sequencing and has increased resolution yet decreased ambiguity in deconvolving cancer subclones and elucidating cancer evolutionary history. ScDNA-seq data is, however, sparse, noisy, and highly variable even within a homogeneous cell population, due to the biases and artifacts that are introduced during the library preparation and sequencing procedure. Here, we propose SCOPE, a normalization and copy number estimation method for scDNA-seq data. The distinguishing features of SCOPE include: (i) utilization of cell-specific Gini coefficients for quality controls and for identification of normal/diploid cells, which are further used as negative control samples in a Poisson latent factor model for normalization; (ii) modeling of GC content bias using an expectation-maximization algorithm embedded in the Poisson generalized linear models, which accounts for the different copy number states along the genome; (iii) a cross-sample iterative segmentation procedure to identify breakpoints that are shared across cells from the same genetic background." –Rujin Wang, Danyu Lin, Yuchao Jiang
seq.hotSPOT	"seq.hotSPOT provides a resource for designing effective sequencing panels to help improve mutation capture efficacy for ultradeep sequencing projects. Using SNV datasets, this package designs custom panels for any tissue of interest and identify the genomic regions likely to contain the most mutations. Establishing efficient targeted sequencing panels can allow researchers to study mutation burden in tissues at high depth without the economic burden of whole-exome or whole-genome sequencing. This tool was developed to make high-depth sequencing panels to study low-frequency clonal mutations in clinically normal and cancerous tissues." –Sydney Grant, Lei Wei, Gyorgy Paragh
seqCNA	"Copy number analysis of high-throughput sequencing cancer data with fast summarization, extensive filtering and improved normalization" –David Mosen-Ansorena
sevenbridges	"R client and utilities for Seven Bridges platform API, from Cancer Genomics Cloud to other Seven Bridges supported platforms." –Phil Webster, Soner Koc, Nan Xiao, Tengfei Yin, Dusan Randjelovic, Emile Young, Velsera

SigCheck	"While gene signatures are frequently used to predict phenotypes (e.g. predict prognosis of cancer patients), it is not always clear how optimal or meaningful they are (cf David Venet, Jacques E. Dumont, and Vincent Detours' paper "Most Random Gene Expression Signatures Are Significantly Associated with Breast Cancer Outcome"). Based on suggestions in that paper, SigCheck accepts a data set (as an ExpressionSet) and a gene signature, and compares its performance on survival and/or classification tasks against a) random gene signatures of the same length; b) known, related and unrelated gene signatures; and c) permuted data and/or metadata." –Rory Stark, Justin Norden
signeR	"The signeR package provides an empirical Bayesian approach to mutational signature discovery. It is designed to analyze single nucleotide variation (SNV) counts in cancer genomes, but can also be applied to other features as well. Functionalities to characterize signatures or genome samples according to exposure patterns are also provided." –Rafael Rosales, Rodrigo Drummond, Renan Valieris, Alexandre Defelicibus, Israel Tojal da Silva
signifinder	"signifinder is an R package for computing and exploring a compendium of tumor signatures. It allows to compute a variety of signatures, based on gene expression values, and return single-sample scores. Currently, signifinder contains 46 distinct signatures collected from the literature, relating to multiple tumors and multiple cancer processes." –Stefania Pirrotta, Enrica Calura
supersigs	"Generate SuperSigs (supervised mutational signatures) from single nucleotide variants in the cancer genome. Functions included in the package allow the user to learn supervised mutational signatures from their data and apply them to new data. The methodology is based on the one described in Afsari (2021, ELife)." –Albert Kuo, Yifan Zhang, Bahman Afsari, Cristian Tomasetti

TRONCO	<p>"The TRONCO (TRanslational ONCOlogy) R package collects algorithms to infer progression models via the approach of Suppes-Bayes Causal Network, both from an ensemble of tumors (cross-sectional samples) and within an individual patient (multi-region or single-cell samples). The package provides parallel implementation of algorithms that process binary matrices where each row represents a tumor sample and each column a single-nucleotide or a structural variant driving the progression; a 0/1 value models the absence/presence of that alteration in the sample. The tool can import data from plain, MAF or GISTIC format files, and can fetch it from the cBioPortal for cancer genomics. Functions for data manipulation and visualization are provided, as well as functions to import/export such data to other bioinformatics tools for, e.g, clustering or detection of mutually exclusive alterations. Inferred models can be visualized and tested for their confidence via bootstrap and cross-validation. TRONCO is used for the implementation of the Pipeline for Cancer Inference (PICNIC)." –Marco Antoniotti, Giulio Caravagna, Luca De Sano, Alex Graudenzi, Giancarlo Mauri, Bud Mishra, Daniele Ramazzotti</p>
Uniquorn	<p>"'Uniquorn' enables users to identify cancer cell lines. Cancer cell line misidentification and cross-contamination represents a significant challenge for cancer researchers. The identification is vital and in the frame of this package based on the locations/ loci of somatic and germline mutations/ variations. The input format is vcf/ vcf.gz and the files have to contain a single cancer cell line sample (i.e. a single member/genotype/gt column in the vcf file)." –Raik Otto</p>
ZygosityPredictor	<p>"The ZygosityPredictor allows to predict how many copies of a gene are affected by small variants. In addition to the basic calculations of the affected copy number of a variant, the Zygosity-Predictor can integrate the influence of several variants on a gene and ultimately make a statement if and how many wild-type copies of the gene are left. This information proves to be of particular use in the context of translational medicine. For example, in cancer genomes, the Zygosity-Predictor can address whether unmutated copies of tumor-suppressor genes are present. Beyond this, it is possible to make this statement for all genes of an organism. The Zygosity-Predictor was primarily developed to handle SNVs and INDELs (later addressed as small-variants) of somatic and germline origin. In order not to overlook severe effects outside of the small-variant context, it has been extended with the assessment of large scale deletions, which cause losses of whole genes or parts of them." –Marco Rheinnecker, Marc Ruebsam, Daniel Huebschmann, Martina Froehlich, Barbara Hutter</p>

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CancerInSilico	"The CancerInSilico package provides an R interface for running mathematical models of tumor progression and generating gene expression data from the results. This package has the underlying models implemented in C++ and the output and analysis features implemented in R." –Thomas D. Sherman, Raymond Cheng, Elana J. Fertig
CancerSubtypes	"CancerSubtypes integrates the current common computational biology methods for cancer subtypes identification and provides a standardized framework for cancer subtype analysis based multi-omics data, such as gene expression, miRNA expression, DNA methylation and others." –Taosheng Xu
IRISFGM	"Single-cell RNA-Seq data is useful in discovering cell heterogeneity and signature genes in specific cell populations in cancer and other complex diseases. Specifically, the investigation of functional gene modules (FGM) can help to understand gene interactive networks and complex biological processes. QUBIC2 is recognized as one of the most efficient and effective tools for FGM identification from scRNA-Seq data. However, its availability is limited to a C implementation, and its applicative power is affected by only a few downstream analyses functionalities. We developed an R package named IRIS-FGM (integrative scRNA-Seq interpretation system for functional gene module analysis) to support the investigation of FGMs and cell clustering using scRNA-Seq data. Empowered by QUBIC2, IRIS-FGM can identify co-expressed and co-regulated FGMs, predict types/clusters, identify differentially expressed genes, and perform functional enrichment analysis. It is noteworthy that IRIS-FGM also applies Seurat objects that can be easily used in the Seurat vignettes." –Yuzhou Chang, Qin Ma, Carter Allen, Dongjun Chung
STROMA4	"This package estimates four stromal properties identified in TNBC patients in each patient of a gene expression datasets. These stromal property assignments can be combined to subtype patients. These four stromal properties were identified in Triple negative breast cancer (TNBC) patients and represent the presence of different cells in the stroma: T-cells (T), B-cells (B), stromal infiltrating epithelial cells (E), and desmoplasia (D). Additionally this package can also be used to estimate generative properties for the Lehmann subtypes, an alternative TNBC subtyping scheme (PMID: 21633166)." –Sadiq Saleh, Michael Hallett

HPAStainR	"This package is built around the HPAStainR function. The purpose of the HPAStainR function is to query the visual staining data in the Human Protein Atlas to return a table of staining ranked cell types. The function also has multiple arguments to personalize to output as well to include cancer data, csv readable names, modify the confidence levels of the results and more. The other functions exist exclusively to easily acquire the data required to run HPAStainR." –Tim O. Nieuwenhuis
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11 Appendix 2 - Bioconductor data packages with 'cancer' in package description

Quoted text is the content of the Description element of the package DESCRIPTION. Names following the text are as reported in the Authors field.

package	desc
antiProfilesData	"Colon normal tissue and cancer samples used in Corrada Bravo, et al. gene expression anti-profiles paper: BMC Bioinformatics 2012, 13:272 doi:10.1186/1471-2105-13-272. Measurements are z-scores obtained from the GeneExpression Barcode in the 'frma' package" –Hector Corrada Bravo, Matthew McCall, Rafael A. Irizarry
BloodCancerMultiOmics2017	"The package contains data of the Primary Blood Cancer Encyclopedia (PACE) project together with a complete executable transcript of the statistical analysis and reproduces figures presented in the paper "Drug-perturbation-based stratification of blood cancer" by Dietrich S, Oles M, Lu J et al., J. Clin. Invest. (2018) 128(1):427-445. doi:10.1172/JCI93801." –Malgorzata Oles, Sascha Dietrich, Junyan Lu, Britta Velten, Andreas Mock, Vladislav Kim, Wolfgang Huber
breastCancerMAINZ	"Gene expression data from the breast cancer study published by Schmidt et al. in 2008, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
breastCancerNKI	"Genexpression data from a breast cancer study published by van't Veer et al. in 2002 and van de Vijver et al. in 2002, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
breastCancerTRANSBIG	"Gene expression data from a breast cancer study published by Desmedt et al. in 2007, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
breastCancerUNT	"Gene expression data from a breast cancer study published by Sotiriou et al. in 2007, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
breastCancerUPP	"Gene expression data from a breast cancer study published by Miller et al. in 2005, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
breastCancerVDX	"Gene expression data from a breast cancer study published by Wang et al. in 2005 and Minn et al. in 2007, provided as an eSet." –Markus Schroeder, Benjamin Haibe-Kains, Aedin Culhane, Christos Sotiriou, Gianluca Bontempi, John Quackenbush
cancerdata	"Dataset for the R package cancerclass" –Jan Budczies, Daniel Kosztyla

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cfToolsData	"The cfToolsData package supplies the data for the cfTools package. It contains two pre-trained deep neural network (DNN) models for the cfSort function. Additionally, it includes the shape parameters of beta distribution characterizing methylation markers associated with four tumor types for the CancerDetector function, as well as the parameters characterizing methylation markers specific to 29 primary human tissue types for the cfDeconvolve function." –Ran Hu, Shuo Li, Xianghong Jasmine Zhou, Wen Yuan Li
CLLmethylation	"The package includes DNA methylation data for the primary Chronic Lymphocytic Leukemia samples included in the Primary Blood Cancer Encyclopedia (PACE) project. Raw data from the 450k DNA methylation arrays is stored in the European Genome-Phenome Archive (EGA) under accession number EGAS0000100174. For more information concerning the project please refer to the paper "Drug-perturbation-based stratification of blood cancer" by Dietrich S, Oles M, Lu J et al., J. Clin. Invest. (2018) and R/Bioconductor package BloodCancerMultiOmics2017." –Malgorzata Oles, Andreas Mock
colonCA	"exprSet for Alon et al. (1999) colon cancer data" –Sylvia Merk
COSMIC.67	"COSMIC: Catalogue Of Somatic Mutations In Cancer, version 67 (2013-10-24)" –Julian Gehring
CRCL18	"colorectal cancer mRNA and miRNA on 18 cell lines" –Claudio Isella
curatedBladderData	"The curatedBladderData package provides relevant functions and data for gene expression analysis in patients with bladder cancer." –Markus Riester
curatedBreastData	"Curated human breast cancer tissue S4 ExpressionSet datasets from over 16 clinical trials comprising over 2,000 patients. All datasets contain at least one type of outcomes variable and treatment information (minimum level: whether they had chemotherapy and whether they had hormonal therapy). Includes code to post-process these datasets." –Katie Planey
curatedCRCData	"The curatedCRC package provides relevant functions and data for gene expression analysis in patients with colorectal cancer." –Princy Parsana, Markus Riester, Curtis Huttenhower, Levi Waldron
curatedOvarianData	"The curatedOvarianData package provides data for gene expression analysis in patients with ovarian cancer." –Benjamin F. Ganzfried, Markus Riester, Steve Skates, Victoria Wang, Thomas Risch, Benjamin Haibe-Kains, Svetlana Tyekucheva, Jie Ding, Ina Jazic, Michael Birrer, Giovanni Parmigiani, Curtis Huttenhower, Levi Waldron

curatedTCGAData	"This package provides publicly available data from The Cancer Genome Atlas (TCGA) as MultiAssayExperiment objects. MultiAssayExperiment integrates multiple assays (e.g., RNA-seq, copy number, mutation, microRNA, protein, and others) with clinical / pathological data. It also links assay barcodes with patient identifiers, enabling harmonized subsetting of rows (features) and columns (patients / samples) across the entire multi-'omics experiment." –Marcel Ramos, Levi Waldron, Lucas Schiffer, Ludwig Geistlinger, Valerie Obenchain, Martin Morgan
depmap	"The depmap package is a data package that accesses datasets from the Broad Institute DepMap cancer dependency study using ExperimentHub. Datasets from the most current release are available, including RNAi and CRISPR-Cas9 gene knockout screens quantifying the genetic dependency for select cancer cell lines. Additional datasets are also available pertaining to the log copy number of genes for select cell lines, protein expression of cell lines as measured by reverse phase protein lysate microarray (RPPA), 'Transcript Per Million' (TPM) data, as well as supplementary datasets which contain metadata and mutation calls for the other datasets found in the current release. The 19Q3 release adds the drug_dependency dataset, that contains cancer cell line dependency data with respect to drug and drug-candidate compounds. The 20Q2 release adds the proteomic dataset that contains quantitative profiling of proteins via mass spectrometry. This package will be updated on a quarterly basis to incorporate the latest Broad Institute DepMap Public cancer dependency datasets. All data made available in this package was generated by the Broad Institute DepMap for research purposes and not intended for clinical use. This data is distributed under the Creative Commons license (Attribution 4.0 International (CC BY 4.0))." –Laurent Gatto, Theo Killian
easierData	"Access to internal data required for the functional performance of easier package and exemplary bladder cancer dataset with both processed RNA-seq data and information on response to ICB therapy generated by Mariathasan et al. "TGF- β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells", published in Nature, 2018 [doi:10.1038/nature25501](https://doi.org/10.1038/nature25501). The data is made available via ['IMvigor210CoreBiologies'](http://research-pub.gene.com/IMvigor210CoreBiologies/) package under the CC-BY license." –Oscar Lapuente-Santana, Federico Marini, Arsenij Ustjanzew, Francesca Finotello, Federica Eduati

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fabiaData	"Supplying gene expression data sets for the demos of the biclustering method "Factor Analysis for Biclust Acquisition" (FABIA). The following three data sets are provided: A) breast cancer (van't Veer, Nature, 2002), B) multiple tissues (Su, PNAS, 2002), and C) diffuse large-B-cell lymphoma (Rosenwald, N Engl J Med, 2002)." –Sepp Hochreiter
gageData	"This is a supportive data package for the software package, gage. However, the data supplied here are also useful for gene set or pathway analysis or microarray data analysis in general. In this package, we provide two demo microarray dataset: GSE16873 (a breast cancer dataset from GEO) and BMP6 (originally published as an demo dataset for GAGE, also registered as GSE13604 in GEO). This package also includes commonly used gene set data based on KEGG pathways and GO terms for major research species, including human, mouse, rat and budding yeast. Mapping data between common gene IDs for budding yeast are also included." –Weijun Luo
GSE62944	"TCGA processed RNA-Seq data for 9264 tumor and 741 normal samples across 24 cancer types and made them available as GEO accession [GSE62944](http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE62944). GSE62944 data have been parsed into a SummarizedExperiment object available in ExperimentHub." –Sonali Arora
GSVAdata	"This package stores the data employed in the vignette of the GSVA package. These data belong to the following publications: Armstrong et al. Nat Genet 30:41-47, 2002; Cahoy et al. J Neurosci 28:264-278, 2008; Carrel and Willard, Nature, 434:400-404, 2005; Huang et al. PNAS, 104:9758-9763, 2007; Pickrell et al. Nature, 464:768-722, 2010; Skaletsky et al. Nature, 423:825-837; Verhaak et al. Cancer Cell 17:98-110, 2010" –Robert Castelo
HarmonizedTCGADData	"This package contains the processed harmonized TCGA data of five cancer types used in "Tianle Ma and Aidong Zhang, Integrate Multi-omic Data Using Affinity Network Fusion (ANF) for Cancer Patient Clustering"." –Tianle Ma
HD2013SGI	"This package contains the experimental data and a complete executable transcript (vignette) of the analysis of the HCT116 genetic interaction matrix presented in the paper "Mapping genetic interactions in human cancer cells with RNAi and multiparametric phenotyping" by C. Laufer, B. Fischer, M. Billmann, W. Huber, M. Boutros; Nature Methods (2013) 10:427-31. doi: 10.1038/nmeth.2436." –Bernd Fischer

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LungCancerACvsSCCGEO	"This package contains 30 Affymetrix CEL files for 7 Adenocarcinoma (AC) and 8 Squamous cell carcinoma (SCC) lung cancer samples taken at random from 3 GEO datasets (GSE10245, GSE18842 and GSE2109) and other 15 samples from a dataset produced by the organizers of the IMPROVER Diagnostic Signature Challenge available from GEO (GSE43580)." –Adi Laurentiu Tarca
LungCancerLines	"Reads from an RNA-seq experiment between two lung cancer cell lines: H1993 (met) and H2073 (primary). The reads are stored as Fastq files and are meant for use with the TP53Genome object in the gmapR package." –Cory Barr, Michael Lawrence
lungExpression	"Data from three large lung cancer studies provided as ExpressionSets" –Robert Scharpf, Simens Zhong, Giovanni Parmigiani
mammaPrintData	"Gene expression data for the two breast cancer cohorts published by Glas and Buyse in 2006. This cohorts were used to implement and validate the mammaPrint breast cancer test." –Luigi Marchionni
mAPKLDData	"Gene expression data from a breast cancer study published by Turashvili et al. in 2007, provided as an eSet." –Argiris Sakellariou
mcsurvdata	"This package stores two merged expressionSet objects that contain the gene expression profile and clinical information of -a- six breast cancer cohorts and -b- four colorectal cancer cohorts. Breast cancer data are employed in the vignette of the hrnbiased package for survival analysis of gene signatures." –Adria Caballe Mestres, Antoni Berenguer Llergo, Camille Stephan-Otto Attolini
MetaGxBreast	"A collection of Breast Cancer Transcriptomic Datasets that are part of the MetaGxData package compendium." –Michael Zon, Deena M.A. Gendoo, Christopher Eeles, Benjamin Haibe-Kains
MetaGxOvarian	"A collection of Ovarian Cancer Transcriptomic Datasets that are part of the MetaGxData package compendium." –Michael Zon, Vandana Sandhu, Christopher Eeles, Benjamin Haibe-Kains
MetaGxPancreas	"A collection of pancreatic Cancer transcriptomic datasets that are part of the MetaGxData package compendium. This package contains multiple pancreas cancer datasets that have been downloaded from various resources and turned into SummarizedExperiment objects. The details of how the authors normalized the data can be found in the experiment data section of the objects. Additionally, the location the data was obtained from can be found in the url variables of the experiment data portion of each SE." –Michael Zon, Vandana Sandhu, Christopher Eeles, Benjamin Haibe-Kains

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microRNAome	"This package provides a SummarizedExperiment object of read counts for microRNAs across tissues, cell-types, and cancer cell-lines. The read count matrix was prepared and provided by the author of the study: Towards the human cellular microRNAome." –Matthew N. McCall, Marc K. Halushka, Arun H. Patil
NGScopyData	"Subset of BAM files of human lung tumor and pooled normal samples by targeted panel sequencing. [Zhao et al 2014. Targeted Sequencing in Non-Small Cell Lung Cancer (NSCLC) Using the University of North Carolina (UNC) Sequencing Assay Captures Most Previously Described Genetic Aberrations in NSCLC. In preparation.] Each sample is a 10 percent random subsample drawn from the original sequencing data. The pooled normal sample has been rescaled according to the total number of normal samples in the "pool". Here provided is the subsampled data on chr6 (hg19)." –Xiaobei Zhao
octad.db	"Open Cancer Therapeutic Discovery (OCTAD) package implies sRGES approach for the drug discovery. The essential idea is to identify drugs that reverse the gene expression signature of a disease by tamping down over-expressed genes and stimulating weakly expressed ones. The following package contains all required precomputed data for whole OCTAD pipeline computation." –E. Chekalin, S. Paithankar, B. Zeng, B. Glicksberg, P. Newbury, J. Xing, K. Liu, A. Wen, D. Joseph, B. Chen
ProData	"A data package of SELDI-TOF protein mass spectrometry data of 167 breast cancer and normal samples." –Xiaochun Li
prostateCancerCamcap	"A Bioconductor data package for the Ross-Adams (2015) Prostate Cancer dataset." –Mark Dunning
prostateCancerGrasso	"A Bioconductor data package for the Grasso (2012) Prostate Cancer dataset." –Mark Dunning
rcellminerData	"The NCI-60 cancer cell line panel has been used over the course of several decades as an anti-cancer drug screen. This panel was developed as part of the Developmental Therapeutics Program (DTP, http://dtp.nci.nih.gov/) of the U.S. National Cancer Institute (NCI). Thousands of compounds have been tested on the NCI-60, which have been extensively characterized by many platforms for gene and protein expression, copy number, mutation, and others (Reinhold, et al., 2012). The purpose of the CellMiner project (http://discover.nci.nih.gov/cellminer) has been to integrate data from multiple platforms used to analyze the NCI-60 and to provide a powerful suite of tools for exploration of NCI-60 data." –Augustin Luna, Vinodh Rajapakse, Fabricio Sousa

RTCGA.clinical	"Package provides clinical datasets from The Cancer Genome Atlas Project for all cohorts types from http://gdac.broadinstitute.org/ . Clinical data format is explained here https://wiki.nci.nih.gov/display/TCGA/Clinical+Data+Overview . Data from 2015-11-01 snapshot." –Marcin Kosinski
RTCGA.CNV	"Package provides CNV (based on Merge snp) datasets from The Cancer Genome Atlas Project for all cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/Retrieving+Data+Using+the+Data+Matrix . Data from 2015-11-01 snapshot." –Przemyslaw Biecek
RTCGA.methylation	"Package provides methylation (humanmethylation27) datasets from The Cancer Genome Atlas Project for all available cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/DNA+methylation Data from 2015-11-01 snapshot." –Marcin Kosinski, Witold Chodor
RTCGA.miRNASeq	"Package provides miRNASeq datasets from The Cancer Genome Atlas Project for all available cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/miRNASeq#miRNASeq-DataOverview Data from 2015-11-01 snapshot." –Witold Chodor
RTCGA.mRNA	"Package provides mRNA datasets from The Cancer Genome Atlas Project for all available cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/Gene+expression+data Data from 2015-11-01 snapshot." –Witold Chodor
RTCGA.mutations	"Package provides mRNA datasets from The Cancer Genome Atlas Project for all available cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/Gene+expression+data Data from 2015-11-01 snapshot." –Witold Chodor
RTCGA.PANCAN12	"Package provides clinical, expression, cnv and mutation data from Genome Cancer Browser." –Przemyslaw Biecek
RTCGA.rnaseq	"Package provides rna-seq datasets from The Cancer Genome Atlas Project for all cohorts types from http://gdac.broadinstitute.org/ . Rna-seq data format is explained here https://wiki.nci.nih.gov/display/TCGA/RNASeq+Version+2 . Data source is illumina hiseq Level 3 RSEM normalized expression data. Data from 2015-11-01 snapshot." –Marcin Kosinski

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RTCGA.RPPA	"Package provides RPPA datasets from The Cancer Genome Atlas Project for all available cohorts types from http://gdac.broadinstitute.org/ . Data format is explained here https://wiki.nci.nih.gov/display/TCGA/Protein+Array+Data+Format+Specification?src=search " –Witold Chodor
SBGNview.data	"This package contains: 1. A microarray gene expression dataset from a human breast cancer study. 2. A RNA-Seq gene expression dataset from a mouse study on IFNG knockout. 3. ID mapping tables between gene IDs and SBGN-ML file glyph IDs. 4. Percent of orthologs detected in other species of the genes in a pathway. Cutoffs of this percentage for defining if a pathway exists in another species. 5. XML text of SBGN-ML files for all pre-collected pathways." –Xiaoxi Dong*, Kovidh Vegesna*, Weijun Luo
seventyGeneData	"Gene expression data for the two breast cancer cohorts published by van't Veer and Van de Vijver in 2002." –Luigi Marchionni, Claudio Zanettini, Lucio Queiroz
SFEData	"Example spatial transcriptomics datasets with Simple Feature annotations as SpatialFeatureExperiment objects. Technologies include Visium, slide-seq, Nanostring CoxMX, Vizgen MERFISH, and 10X Xenium. Tissues include mouse skeletal muscle, human melanoma metastasis, human lung, breast cancer, and mouse liver." –Lambda Moses, Kayla Jackson, Lior Pachter
shinyMethylData	"Extracted data from 369 TCGA Head and Neck Cancer DNA methylation samples. The extracted data serve as an example dataset for the package shinyMethyl. Original samples are from 450k methylation arrays, and were obtained from The Cancer Genome Atlas (TCGA). 310 samples are from tumor, 50 are matched normals and 9 are technical replicates of a control cell line." –Jean-Philippe Fortin, Kasper Daniel Hansen
SomatiCAData	"An example cancer whole genome sequencing data for the SomatiCA package" –Mengjie Chen
SomaticCancerAlterations	"Collection of somatic cancer alteration datasets" –Julian Gehring
stjudem	"This is a microarray data set on acute lymphoblastic leukemia, published in 2002 (Yeoh et al. Cancer Cell 2002). The experiments were conducted in the St. Jude Children's Research Hospital, Memphis, Tennessee, USA. The raw data was preprocessed by variance stabilizing normalization (Huber et al.) on probe and subsequent summarization of probe expression values into probe set expression values using median polish." –Benjamin Georgi, Matthias Heinig, Sebastian Schmeier, Joern Toedling
TCGAcrmiRNA	"colorectal cancer miRNA profile provided by TCGA" –Claudio Isella
TCGAcrRNA	"colorectal cancer mRNA profile provided by TCGA" –Claudio Isella

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TCGAMethylation450k	"The Cancer Genome Atlas (TCGA) is applying genomics technologies to over 20 different types of cancer. This package contains a small set of 450k array data in idat format." –Sean Davis
TCGAWorkflowData	"This experimental data package contains 11 data sets necessary to follow the "TCGA Workflow: Analyze cancer genomics and epigenomics data using Bioconductor packages". " –Tiago Chedraoui Silva

12 Appendix 3 - Software packages used in the construction of Figure 7

package	version	date(UTC)	source
abind	1.4-5	2016-07-21	RSPM (R 4.2.0)
AnnotationDbi	1.64.1	2023-11-03	Bioconductor
AnnotationHub	3.10.0	2023-10-24	Bioconductor
backports	1.4.1	2021-12-13	RSPM (R 4.2.0)
bcclViper	1.38.0	2023-10-26	Bioconductor
Biobase	2.62.0	2023-10-24	Bioconductor
BiocFileCache	2.10.1	2023-10-26	Bioconductor
BiocGenerics	0.48.1	2023-11-01	Bioconductor
BiocManager	1.30.22	2023-08-08	RSPM (R 4.2.0)
BiocParallel	1.36.0	2023-10-24	Bioconductor
BiocVersion	3.18.0	2023-04-25	Bioconductor
Biostrings	2.70.1	2023-10-25	Bioconductor
bit	4.0.5	2022-11-15	RSPM (R 4.2.0)
bit64	4.0.5	2020-08-30	RSPM (R 4.2.0)
bitops	1.0-7	2021-04-24	RSPM (R 4.2.0)
blob	1.2.4	2023-03-17	RSPM (R 4.2.0)
broom	1.0.5	2023-06-09	RSPM (R 4.2.0)
bspm	0.5.5	2023-08-22	CRAN (R 4.3.1)
cachem	1.0.8	2023-05-01	RSPM (R 4.2.0)
car	3.1-2	2023-03-30	RSPM (R 4.2.0)
carData	3.0-5	2022-01-06	RSPM (R 4.2.0)
class	7.3-22	2023-05-03	RSPM (R 4.2.0)
cli	3.6.2	2023-12-11	RSPM (R 4.3.0)
codetools	0.2-19	2023-02-01	RSPM (R 4.2.0)
coin	1.4-3	2023-09-27	RSPM (R 4.3.0)
colorspace	2.1-0	2023-01-23	RSPM (R 4.2.0)
cowplot	1.1.2	2023-12-15	RSPM (R 4.3.0)
crayon	1.5.2	2022-09-29	RSPM (R 4.2.0)
curl	5.2.0	2023-12-08	RSPM (R 4.3.0)
data.table	1.14.10	2023-12-08	RSPM (R 4.3.0)
DBI	1.1.3	2022-06-18	RSPM (R 4.2.0)
dbplyr	2.4.0	2023-10-26	RSPM (R 4.3.0)
decoupleR	2.8.0	2023-10-24	Bioconductor
DelayedArray	0.28.0	2023-10-24	Bioconductor
DESeq2	1.42.0	2023-10-24	Bioconductor
digest	0.6.33	2023-07-07	RSPM (R 4.2.0)
dorothea	1.14.0	2023-10-26	Bioconductor
dplyr	1.1.4	2023-11-17	RSPM (R 4.3.0)
e1071	1.7-14	2023-12-06	RSPM (R 4.3.0)
easier	1.8.0	2023-10-24	Bioconductor
easierData	1.8.0	2023-10-26	Bioconductor
ellipsis	0.3.2	2021-04-29	RSPM (R 4.2.0)

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evaluate	0.23	2023-11-01	RSPM (R 4.3.0)
ExperimentHub	2.10.0	2023-10-24	Bioconductor
fansi	1.0.6	2023-12-08	RSPM (R 4.3.0)
farver	2.1.1	2022-07-06	RSPM (R 4.2.0)
fastmap	1.1.1	2023-02-24	RSPM (R 4.2.0)
filelock	1.0.3	2023-12-11	RSPM (R 4.3.0)
generics	0.1.3	2022-07-05	RSPM (R 4.2.0)
GenomeInfoDb	1.38.1	2023-11-08	Bioconductor
GenomeInfoDbData	1.2.11	<NA>	Bioconductor
GenomicRanges	1.54.1	2023-10-29	Bioconductor
ggplot2	3.4.4	2023-10-12	RSPM (R 4.3.0)
ggpubr	0.6.0	2023-02-10	RSPM (R 4.2.0)
ggrepel	0.9.4	2023-10-13	RSPM (R 4.3.0)
ggsignif	0.6.4	2022-10-13	RSPM (R 4.2.0)
glue	1.6.2	2022-02-24	RSPM (R 4.2.0)
gridExtra	2.3	2017-09-09	RSPM (R 4.2.0)
gtable	0.3.4	2023-08-21	RSPM (R 4.2.0)
htmltools	0.5.7	2023-11-03	RSPM (R 4.3.0)
htmlwidgets	1.6.4	2023-12-06	RSPM (R 4.3.0)
httpuv	1.6.13	2023-12-06	RSPM (R 4.3.0)
httr	1.4.7	2023-08-15	RSPM (R 4.2.0)
interactiveDisplayBase	1.40.0	2023-10-24	Bioconductor
IRanges	2.36.0	2023-10-24	Bioconductor
jsonlite	1.8.8	2023-12-04	RSPM (R 4.3.0)
KEGGREST	1.42.0	2023-10-24	Bioconductor
kernlab	0.9-32	2023-01-31	RSPM (R 4.2.0)
KernSmooth	2.23-22	2023-07-10	RSPM (R 4.2.0)
knitr	1.45	2023-10-30	RSPM (R 4.3.0)
labeling	0.4.3	2023-08-29	RSPM (R 4.2.0)
later	1.3.2	2023-12-06	RSPM (R 4.3.0)
lattice	0.22-5	2023-10-24	RSPM (R 4.3.0)
lazyeval	0.2.2	2019-03-15	RSPM (R 4.2.0)
libcoin	1.0-10	2023-09-27	RSPM (R 4.3.0)
lifecycle	1.0.4	2023-11-07	RSPM (R 4.3.0)
limSolve	1.5.7	2023-09-21	RSPM (R 4.3.0)
locfit	1.5-9.8	2023-06-11	RSPM (R 4.2.0)
lpSolve	5.6.20	2023-12-10	RSPM (R 4.3.0)
magrittr	2.0.3	2022-03-30	RSPM (R 4.2.0)
MASS	7.3-60	2023-05-04	RSPM (R 4.2.0)
Matrix	1.6-4	2023-11-30	RSPM (R 4.3.0)
MatrixGenerics	1.14.0	2023-10-24	Bioconductor
matrixStats	1.2.0	2023-12-11	RSPM (R 4.3.0)
memoise	2.0.1	2021-11-26	RSPM (R 4.2.0)
mime	0.12	2021-09-28	RSPM (R 4.2.0)
mixtools	2.0.0	2022-12-05	RSPM (R 4.2.0)
modeltools	0.2-23	2020-03-05	RSPM (R 4.2.0)
multcomp	1.4-25	2023-06-20	RSPM (R 4.2.0)
munsell	0.5.0	2018-06-12	RSPM (R 4.2.0)

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mvtnorm	1.2-4	2023-11-27	RSPM (R 4.3.0)
nlme	3.1-164	2023-11-27	RSPM (R 4.3.0)
pillar	1.9.0	2023-03-22	RSPM (R 4.2.0)
pkgconfig	2.0.3	2019-09-22	RSPM (R 4.2.0)
plotly	4.10.3	2023-10-21	RSPM (R 4.3.0)
plyr	1.8.9	2023-10-02	RSPM (R 4.3.0)
png	0.1-8	2022-11-29	RSPM (R 4.2.0)
preprocessCore	1.64.0	2023-10-24	Bioconductor
progeny	1.24.0	2023-10-24	Bioconductor
promises	1.2.1	2023-08-10	RSPM (R 4.2.0)
proxy	0.4-27	2022-06-09	RSPM (R 4.2.0)
purrr	1.0.2	2023-08-10	RSPM (R 4.2.0)
quadprog	1.5-8	2019-11-20	RSPM (R 4.2.0)
quantiseqr	1.10.0	2023-10-24	Bioconductor
R6	2.5.1	2021-08-19	RSPM (R 4.2.0)
rappdirs	0.3.3	2021-01-31	RSPM (R 4.2.0)
Rcpp	1.0.11	2023-07-06	RSPM (R 4.2.0)
RCurl	1.98-1.13	2023-11-02	RSPM (R 4.3.0)
reshape2	1.4.4	2020-04-09	CRAN (R 4.0.1)
rlang	1.1.2	2023-11-04	RSPM (R 4.3.0)
rmarkdown	2.25	2023-09-18	RSPM (R 4.3.0)
ROCR	1.0-11	2020-05-02	RSPM (R 4.2.0)
RSQLite	2.3.4	2023-12-08	RSPM (R 4.3.0)
rstatix	0.7.2	2023-02-01	RSPM (R 4.2.0)
S4Arrays	1.2.0	2023-10-24	Bioconductor
S4Vectors	0.40.2	2023-11-23	Bioconductor 3.18 (R 4.3.2)
sandwich	3.1-0	2023-12-11	RSPM (R 4.3.0)
scales	1.3.0	2023-11-28	RSPM (R 4.3.0)
segmented	2.0-1	2023-12-19	RSPM (R 4.3.0)
sessioninfo	1.2.2	2021-12-06	RSPM (R 4.2.0)
shiny	1.8.0	2023-11-17	RSPM (R 4.3.0)
SparseArray	1.2.2	2023-11-07	Bioconductor
startup	0.21.0	2023-12-11	RSPM (R 4.3.0)
stringi	1.8.3	2023-12-11	RSPM (R 4.3.0)
stringr	1.5.1	2023-11-14	RSPM (R 4.3.0)
SummarizedExperiment	1.32.0	2023-10-24	Bioconductor
survival	3.5-7	2023-08-14	RSPM (R 4.2.0)
TH.data	1.1-2	2023-04-17	RSPM (R 4.2.0)
tibble	3.2.1	2023-03-20	RSPM (R 4.3.0)
tidyr	1.3.0	2023-01-24	RSPM (R 4.2.0)
tidyselect	1.2.0	2022-10-10	RSPM (R 4.2.0)
utf8	1.2.4	2023-10-22	RSPM (R 4.3.0)
vctrs	0.6.5	2023-12-01	RSPM (R 4.3.0)
viper	1.36.0	2023-10-24	Bioconductor
viridisLite	0.4.2	2023-05-02	RSPM (R 4.2.0)
withr	2.5.2	2023-10-30	RSPM (R 4.3.0)
xfun	0.41	2023-11-01	RSPM (R 4.3.0)
xtable	1.8-4	2019-04-21	RSPM (R 4.2.0)

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XVector	0.42.0	2023-10-24	Bioconductor
yaml	2.3.8	2023-12-11	RSPM (R 4.3.0)
zlibbioc	1.48.0	2023-10-24	Bioconductor
zoo	1.8-12	2023-04-13	RSPM (R 4.2.0)

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